Appendix 2 Characteristics of included studies

Study characteristics are tabulated in alphabetical order by the first author's surname.

Abbreviations are listed at the end of each section.

Included studies

The main characteristics of the studies are tabulated in alphabetical order by the first author's surname.

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Included studies

Akhouri 2023

Author Reference	Akhouri et al. [1]
Year	2023
Country	India
Study Design	Longitudinal prospective RCT study.
Setting	Outpatient and inpatient departments of Department of Psychiatry, Jawaharlal Nehru Medical College and Hospital (JNMCH), Aligarh, Uttar Pradesh, India.
Population	156 patients diagnosed with post-COVID-19 depression; age 18-60 years; both males and females; literate and illiterate; post-COVID-19 symptoms after 3–4 weeks of discharge.
Inclusion criteria	Diagnosed with depression per DSM-5; age 18-60 years; literate or illiterate; males and females; gave consent; no history of depression.
Exclusion criteria	Age below 18 or above 60; psychiatric or comorbid disorders; intellectual disability; visual/hearing impairments; previous episodes of depression or mood disorders.
Interventions Participants (n) Drop-outs (n)	Experimental group received pharmacotherapy plus eight sessions of CBT (psychoeducation, relaxation breathing exercise, cognitive restructuring, activity scheduling). 92 Not mentioned.
Control Participants (n)	Control group received pharmacotherapy only. 64

Drop-outs (n)	Not mentioned.
Follow up time points	Pre- and post-intervention assessments using Beck Depression Inventory-II (BDI-II).
Outcomes Measured	Severity of depression assessed via BDI-II.
Results	Pre-intervention depression levels (BDI-II scores), mean (SD): - Experimental group: 33.47 (10.24) - Control group: 36.06 (9.48) Post-intervention depression levels, mean (SD): - Experimental group: 8.34 (1.96) - Control group: 15.06 (4.45) Comparison between pre- and post-intervention scores in experimental and control groups: - Significant improvement was found in both groups ($p<0.000$), but the experimental group showed far greater reduction in depressive symptoms. - Between-group comparison post intervention showed that CBT combined with medication was significantly more effective than medication alone ($t = -12.69$, $p<0.000$).
Limitations Noted	Modest sample size; single hospital setting; no family history of depression recorded; no follow-up after therapy termination; unable to separate effects of CBT from pharmacotherapy.
Risk of bias	Moderate

Bai 2024

Author Reference	Bai et al. [2]
Year	2024
Country	China
Study Design	Randomized controlled trial (single-center, parallel-group, open-label).

Setting	Cardiac rehabilitation clinic at Guangdong Provincial People's Hospital, Southern Medical University, Guangzhou, China.
Population	24 patients aged 18–75 years (mean age 46.5 years) with long COVID symptom such as fatigue, cognitive impairment, chest discomfort, etc., persisting ≥2 months post-infection; 58.3% female; median time from COVID-19 diagnosis to enrollment was 14 weeks.
Inclusion criteria	History of SARS-CoV-2 infection; symptoms persisting ≥2 months post-infection; positive RT-PCR or antigen test with negative result ≥4 weeks before inclusion; symptoms include at least one of such as cough, fatigue, cognitive impairment, chest tightness, palpitations, etc.
Exclusion criteria	Conditions worsened by exercise (acute cardiac insufficiency, exercise-induced asthma, epilepsy); serious comorbidities (unstable angina, oxygen saturation <93%, uncontrolled arrhythmia, uncontrolled hypertension or type 2 diabetes); physical disabilities due to bone/joint or neuromuscular diseases; pregnancy or lactation.
Intervention Participants (n) Drop-outs (n)	Training group 4-week supervised aerobic training on cycling ergometer, 3 sessions/week (12 sessions total), using moderate- or high-intensity interval training based on peak VO2 and work rate. n=12 n=0
Control Participants (n) Drop-outs (n)	Control group: standard healthy lifestyle guidance and WHO self-management recommendations. n=12 n=0

Follow up time points	Baseline and 4 weeks (post-intervention) assessments using CPET and questionnaires (SF-12, PHQ-9, GAD-7, ISI, Perceived Stress Scale).
Outcomes Measured	Primary: Changes in persistent symptoms (total number, specific symptoms). Secondary: Cardiopulmonary fitness (peak VO2, AT VO2, exercise time, maximum load, O2 pulse, HRmax) and mental health (PHQ-9, GAD-7, stress, insomnia, SF-12 scores).
Results	Results reported for between group differences: Reduced number of persistent symptoms: 67.8% (n=8 patients) in training group vs 16.2% (n=2 patients) in control group after 4 weeks (p=0.013). SF-12, sub scores of mental components (MCS) and physical component (PCS): non-significant. PHQ-9 (depressive symptoms): non-significant. GAD-7 (anxiety symptoms): non-significant. Results from cardiopulmonary fitness and function: Improvement in exercise time: 80.34 s vs. 20.83 s in favor of training group (p for group x time = 0.028). Improvement in maximum load (mean change, watt): 20.25 vs. 3.83 in favor of training group (p for group x time = 0.01). Peak VO_2 improved in the training group (mean change, mL/kg/

	Min): 4.64 vs.- 1.06; (p for group x time = 0.041). There were no significant differences in changes between groups for pulmonary function. Additional outcomes were reported.
Limitations Noted	Small sample size; single center; short duration (4 weeks) with no long-term follow-up; lack of stratified analysis for comorbidities; no detailed scale assessment of baseline exercise habits.
Risk of bias	Moderate

Besnier 2025 and Gaudreau-Majeau 2024

Author Reference	Two articles reporting results from same study: Besnier et al. [3] Gaudreau-Majeau et al. [4]
Year	2025
Country	Canada
Study Design	Randomized controlled trial (two-arm, parallel-group).
Setting	Centre ÉPIC, Montreal Heart Institute, Montreal, Quebec, Canada.
Population	40 individuals with long COVID; mean age 53; symptoms persisting ≥3 months post-infection; included fatigue, breathlessness, cognitive issues; 72% female in control group and 65% female in rehabilitation group.
Inclusion criteria	Age ≥40 years; positive PCR test for SARS-CoV-2; persistent dyspnea and/or fatigue ≥3 months after infection; 1-point increase in dyspnea on Modified Medical Research Council scale compared to pre-infection period; no contraindication to exercise rehabilitation testing/training; able to give informed consent.
Exclusion criteria	Pulmonary embolism; contraindications to cardiopulmonary stress tests/exercise training; severe exercise intolerance; significant myocardial ischemia or arrhythmia; severe pulmonary hypertension; severe respiratory disease; recent cardiovascular events; heart failure NYHA III/IV; kidney failure requiring dialysis.
Intervention Participants (n) Drop-outs (n)	Rehabilitation group 8-week individualized, supervised cardiopulmonary rehabilitation (3 sessions/week of aerobic + resistance + daily inspiratory muscle training). n=20 n=2 in Besnier et al

	n=5 in Gaudreau-Majeau et al.
Control Participants (n) Drop-outs (n)	Control group maintained daily habits; rehabilitation offered after study completion. n=20 n=3
Follow up time points	Baseline and 8 weeks post-intervention assessments (CPET, functional tests, quality of life questionnaires including SF-36, Post-COVID Functional Scale, Medical Research Council Breathlessness Scale, and symptom impact tools).
Outcomes Measured	Primary: Change in VO2 peak (mL/kg/min) via CPET. Secondary: Submaximal CPET parameters (VE/VCO2 slope, ventilatory thresholds), functional tests (6-Min Walking Test, Timed Up and Go, Sit-to-Stand), quality of life (SF-36 physical and mental component scores), and symptom impact scales (personal, family, professional, social life, mood).
Results	Primary outcomes Besnier et al. VO_2 peak after 8 weeks (mL.kg.min) 22.82 ± 5.57 vs. 18.62 ± 3.77 in favor for rehabilitation group. Effect corresponds to Hedge's g of 0.477 (p=0.003) (Several V02 outcomes, but VO_2 peak is highlighted by authors. Consistency in VO2 results). Secondary outcomes Spirometry: FVC (L) no statistically significant differences between groups (p=0.350) Physical functioning:

	6MWT (m): 548.9 ± 130.3 vs. 482.5 ± 81.1 at 8 weeks in favor of rehabilitation group. P=0.010. TUG usual speed (seconds): 6.99 ± 1.39 vs 8.22 ± 2.25 in favor of rehabilitation group (p=0.031). TUG fast speed (seconds): 5.56 ± 1.32 vs 6.26 ± 1.42 (p=0.066). Functional scales: PCFS category, trend towards improvement in rehabilitation group (p=0.063). MRC dyspnea scale, statistically significant improvement in rehabilitation group (p=0.43). Quality of life (SF-36) No statistically significant difference in physical functioning. No statistically significant differences in Physical Component scale (PCS) and Mental Component Scale (MCS). Additional outcomes were reported. In each session, an adapted version of the Cotler's questionnaire was administered to assess post exertional malaise. Primary outcomes Gaudreau-Majeau et al. Neuropsychological tests evaluating episodic memory, executive functions, processing speed, cognition (MoCA), working memory, anxiety inventory and sleep quality (PSQI), all with no statistically significant differences at follow-up. Symptoms of geriatric depression (12.14 ± 8.55 vs 14.38 ± 7.88, p=0.015) and perceived stress (15.86 ± 8.31 vs 18.80 ±

	10.28, p=0.002) resulted in statistically significant improvements in rehabilitation group compared to control. Additional outcomes were reported.
Limitations Noted	Small sample size; predominantly Caucasian participants; short follow-up (8 weeks); lack of evaluation of alternative rehabilitation modalities; no stratified analysis for sex differences; potential variability from SARS-CoV-2 variants and vaccination status. Authors state that missing values were not imputed, and analysis was conducted on an intention-to-treat basis. It seems analysis was performed on complete cases only.
Risk of bias	Moderate

Campos 2024

Author Reference	Campos et al. [5]
Year	2024
Country	Brazil
Study Design	Pragmatic randomized double-blind clinical trial.
Setting	Dental clinic at Nove de Julho University, São Paulo, Brazil.
Population	40 adult participants (18–64 years) (mean age: intervention 44 years; control 40 years) with persistent orofacial pain and/or tension-type headache >3 months post-COVID-19 infection confirmed by RT-PCR; 34 participants analyzed (per-protocol and ITT).
Inclusion criteria	Adults (18–64 years); confirmed SARS-CoV-2 infection by RT-PCR; recovered at least 30 days; persistent orofacial pain or tension-type headache for >3 months.
Exclusion criteria	Neuropathy or headache types other than tension-type headache; physical or intellectual inability to complete questionnaires; illiteracy; diabetes; pacemaker; pregnancy; laser photosensitivity.

Intervention	VPBM group: 4 weekly sessions (30 min each) of vascular photobiomodulation (660 nm red laser, 100 mW) applied to radial artery using ECCO Reability device.
Participants (n)	n=14
Drop-outs (n)	n=2
Control	Sham VPBM group: same protocol with inactive PBM device emitting conventional red light.
Participants (n)	n=20
Drop-outs (n)	n=4
Follow up time points	Baseline, weekly (VAS and BPI), and after 4 weeks (HIT-6, VAS, BPI) assessments.
Outcomes Measured	Primary: Pain intensity (VAS; BPI). Secondary: Headache impact on activities (HIT-6); pain interference in walking, work, sleep, enjoyment of life.
Results	Primary outcome (ITT) Pain intensity (BPI): no ITT-data reported Pain intensity (VAS): significant reduction in both groups at end-of-treatment, but not statistically significant between-group difference (p = 0.189). Secondary outcome (ITT) Headache impact on activities (HIT-6): no significant between-group difference; p-value not reported. (Per protocol results not tabulated by SBU).

Limitations Noted	Small sample size; convenience sample; short follow-up (4 weeks); first clinical trial of VPBM for post-COVID-19 OFP and TTH; challenges in defining specific protocol; potential dropouts due to daily life factors. The ITT analysis was limited to those 34 of the 40 included participants who underwent at least two of the four treatment sessions (data imputed using last observation carried forward).
Risk of bias	Moderate

Charoenporn 2024

Author Reference	Charoenporn et al. [6]
Year	2024
Country	Thailand
Study Design	Randomized controlled trial (double-blind, placebo-controlled).
Setting	Thammasat University Hospital, Thailand.
Population	80 adults aged 18–60 (mean age 34 years) with post-COVID fatigue or neuropsychiatric symptoms ≥1 month and ≤12 months after COVID-19; 77.5% female; mostly vaccinated.
Inclusion criteria	Confirmed COVID-19 within past 12 months using PCR or antigen testing; ≥1 post-COVID symptom (fatigue, anxiety, depression, sleep disturbance, or cognitive impairment) starting within 3 months of infection and persisting ≥1 month; no residual common cold symptoms.
Exclusion criteria	Pre-existing bipolar disorder, major depression, anxiety disorder, schizophrenia, or dementia; vitamin D supplementation in past month; serum 25(OH)D >50 ng/mL; serum calcium >10.5 mg/dL; pregnancy or lactation; contraindications to vitamin D.

Intervention Participants (n) Drop-outs (n)	Vitamin D group: 60,000 IU oral vitamin D2 weekly for 8 weeks (total 480,000 IU). Regular phone check-ins for adherence. n=40 n=0
Control Participants (n) Drop-outs (n)	Placebo group: starch capsule weekly for 8 weeks. Regular phone check-ins for adherence. n=40 n=2 (missing blood outcomes; questionnaire data complete).
Follow up time points	Baseline, 4 weeks, and 8 weeks (end of intervention) assessments (fatigue, anxiety, depression, sleep quality, cognitive tests, inflammatory markers).
Outcomes Measured	Primary: Changes in fatigue (CFQ-11), anxiety/depression (DASS-21), sleep quality (PSQI), cognition (ACE-III, TMT-A and TMT-B). Secondary: adverse events.
Results	Coefficients of adjusted between-group differences at 8 weeks. Primary outcomes: Fatigue (CFQ-11): statistically significant reduction in favor of intervention group, -3.5 (p=0.024). Depression (DASS-depression): no statistically significant difference, -1.7 (p=0.085).

	Anxiety (DASS-anxiety): significant reduction in favor of intervention group, -2.0 (p=0.011). Sleep quality (PSQI): no statistically significant difference, -1.2 (p=0.052). Cognition (ACE-III): statistically significant improvement in favor of intervention group, 2.1 (p=0.012). Cognition (TMT-A/B): no statistically significant difference, -6.9 (p=0.161). Secondary outcomes: Adverse events: The incidence of adverse events was comparable between the treatment and control groups, with no reports of any serious adverse events.
Limitations Noted	Small sample size; short follow-up (8 weeks); predominance of young female participants; use of vitamin D2 (less potent than D3); subacute and chronic PCS phases mixed; generalizability limited.
Risk of bias	Low

DelCorral 2025

Author Reference	del Corral et al. [7]
Year	2025
Country	Spain
Study Design	Randomized controlled trial (parallel, double-blind).

Setting	University Hospital 12 de Octubre, Madrid, Spain (Rehabilitation Department and Post-COVID Rehabilitation Unit).
Population	64 adults (mean age ~50 years; 64% female) with long-term post-COVID-19 symptoms (fatigue, dyspnoea) persisting ≥3 months post-infection.
Inclusion criteria	≥18 years old; confirmed SARS-CoV-2 by PCR; long-term post-COVID symptoms ≥3 months; fatigue and dyspnoea.
Exclusion criteria	Underlying cardiopulmonary, neuromuscular, neurological, psychiatric, or cognitive conditions; contraindications to exercise; previous rehabilitation participation; lack of internet access.
Intervention Participants (n) Drop-outs (n)	AE+RMT: 8-week aerobic exercise (50 min/session, 2×/week) plus home-based respiratory muscle training (3×/week, 40 min/session) with real device. n=32 n=2
Control Participants (n) Drop-outs (n)	AE+RMTsham group: same aerobic exercise plus sham RMT device. n=32 n=3
Follow up time points	Baseline and 8 weeks post-intervention (end of program) assessments.
Outcomes Measured	Primary: Health-related quality of life (EQ-5D-5L) and exercise tolerance (CPET; peak VO2). Secondary: respiratory muscle strength (MIP, MEP, IME); lung function (spirometry, (DLCO); peripheral muscle strength (1-

	min (STS), handgrip), psychological status (HADS anxiety/depression).
Results	Adjusted between-group difference at 8 weeks (95%CI); Cohen's d. Primary outcomes: Health-related quality of life (EQ-5D-5L, index): no statistically significant difference, 0.06 (−0.01 to 0.13); d=0.3. Health-related quality of life (EQ-5D-5L, VAS): no statistically significant difference, 6.35 (−1.3 to14.0); d=0.4. Exercise tolerance (CPET; peak VO2): no statistically significant difference, 0.4 (−0.5 to 1.3); d=0.2. Secondary outcomes: Respiratory muscle strength (MIP): statistically significant improvement in favor of intervention group, 17.9 (10.4 to 25.4); d=1.2. Respiratory muscle strength (MEP): statistically significant improvement in favor of intervention group, 29.4 (17.7 to 41.1); d=1.3. Respiratory muscle strength (IME): statistically significant improvement in favor of intervention group, 9.0 (3.0 to 15.0); d=0.7. Lung function (spirometry): no statistically significant differences (FEV, FVC, FEV/FVC) except for peak expiratory flow (PEF) which showed a statistically significant

	improvement in favor of intervention group, 0.6 (0.02 to 1.3); d=0.4. Peripheral muscle strength (1-min STS): no statistically significant differences, 1.6 (−1.3 to 4.5); d=0.3. Peripheral muscle strength (handgrip): no statistically significant differences, −0.2 (−2.2 to 1.8); d=0.1. Psychological status, anxiety (HADS-Anxiety): no statistically significant differences, −0.04 (−1.5 to 1.4); d=0.1. Psychological status, depression (HADS-Depression): no statistically significant differences, −0.2 (−1.5 to 1.2); d=0.1. Psychological status, distress (HADS-Total): no statistically significant differences): −0.3 (−2.7 to 2.2); d=0.1.
Limitations Noted	Short duration (8 weeks); small sample size; single center; limited generalizability to children or elderly; partial unblinding in some participants; no long-term follow-up.
Risk of bias	Low

Duffy 2024

Author Reference	Duffy et al. [8]
Year	2024
Country	USA
Study Design	Randomized controlled trial (single-blinded).

Setting	Thomas Jefferson University Hospital and Monell Chemical Senses Center, Philadelphia, Pennsylvania, USA.
Population	83 adults (mean age 50 ± 15 years; 71% female) with persistent olfactory dysfunction (OD) ≥6 months post-COVID-19.
Inclusion criteria	Adults ≥18 years; COVID-19 positive (PCR or at-home test); OD duration ≥6 months; BSIT ≤8/12 or SCENTinel ≤40/100%.
Exclusion criteria	Pre-existing OD (trauma, iatrogenic, idiopathic); active rhinosinusitis; skull-base tumors; malignancies; coagulopathies; thrombocytopenia; antiplatelet/blood thinning medication; nasal surgery during study period; pathology leading to obstruction of olfactory cleft.
Intervention Participants (n) Drop-outs (n)	PRP group: three monthly topical applications of platelet-rich plasma (PRP)-coated Surgifoam to bilateral olfactory clefts. n=42 n=0
Control Participants (n) Drop-outs (n)	Placebo group: identical protocol using saline-coated Surgifoam. n=43 n=2
Follow up time points	Baseline; monthly assessments during 3 months of treatment; remote monthly follow-up from months 4 to 12.
Outcomes Measured	Primary: Change in BSIT scores. Secondary: SCENTinel odor intensity and Questionnaire of Olfactory Disorders—Negative Statements (QOD-NS) for quality of life.
Results	I: n=42, C: n=41 Smell identification (changes in BSIT scores from baseline): PRP-group experienced a significant increase in scores

	compared to placebo from month 1 to months 5, 6, 7, 8, 9, and 12 (p<0.05 for all). Smell identification (total BSIT scores): Despite a greater improvement in BSIT scores from baseline, total BSIT scores were similar between the two groups throughout the study (p=0.264). Odor intensity (SCENTinel odor intensity): no significant differences between groups over time or from baseline (p>0.05). Quality of life (change in QOD-NS from baseline): no statistically significant difference between groups. No adverse events were observed.
Limitations Noted	Use of BSIT (lower fidelity than Sniffin Sticks); subjective SCENTinel measures; significant attrition during remote follow-up; short follow-up period; small sample size; lack of threshold/discrimination testing.
Risk of bias	Moderate

Dwiputra 2024

Author Reference	Dwiputra et al. [9]
Year	2024
Country	Indonesia
Study Design	Randomized controlled trial (single-blind).
Setting	National Cardiovascular Center Harapan Kita (NCCHK), Jakarta, Indonesia.

Population	46 adults with long COVID and cardiovascular comorbidities; mean age ~55 years; 52% male; symptoms persisting >30 days post-COVID-19 diagnosis.
Inclusion criteria	History of positive COVID-19 infection confirmed by a PCR test; persistent symptoms ≥30 days; cardiovascular comorbidities (hypertensive heart disease, coronary artery disease (CAD), heart failure, congenital heart disease, post-operative cardiac surgeries).
Exclusion criteria	Chronic obstructive pulmonary disease, stroke, severe musculoskeletal impairment (e.g., fracture, amputation, severe lower extremity arthritis).
Intervention Participants (n) Drop-outs (n)	Intervention group: Home-based breathing and chest mobility exercises 3×/week for 12 weeks plus home-based cardiac rehabilitation (brisk walking 5×/week, 30 min). n=23 n=1
Control Participants (n) Drop-outs (n)	Control group: Home-based cardiac rehabilitation only (brisk walking 5×/week, 30 min). n=23 n=2
Follow up time points	Baseline and post-intervention (12 weeks) assessments.
Outcomes Measured	Primary: Cardiorespiratory functional capacity (6-MWT; PEFR; PCF; predicted VO2 peak). Secondary: EuroQoL.
Results	Between-group difference (95% CI) at 12 weeks: Primary outcomes:

	Cardiopulmonary functional status: 6-MWT distance: statistically significant improvement in favor of intervention group, 52.39 (4.81-99 96). PEFR, L/min: statistically significant improvement in favor of intervention group, 91.30 (8.61-173.99). PCF, L/min: statistically significant improvement in favor of intervention group, 99.56 (19.91-179.21). Predicted VO2 peak, mUkg/min: no statistically significant difference between groups. Secondary outcomes: Quality of life (EuroQoL score, %): no statistically significant difference between groups. No major cardiovascular events nor adverse effects related to the study were observed. Additional outcomes were reported.
Limitations Noted	Remote monitoring limited exercise supervision; VO2 peak were estimated, not measured via CPET; resource constraints; single center; modest sample size.
Risk of bias	Moderate

Geng 2024

Author Reference	Geng et al. [10]
Year	2024
Country	USA
Study Design	Randomized controlled trial (double-blind, placebo-controlled).
Setting	Stanford University, USA.
Population	155 adults with post-acute sequelae of SARS-CoV-2 infection (PASC); mean age ~45 years; females 59%; diverse demographic (Asian, Black, Hispanic, White); symptomatic ≥3months post-COVID.
Inclusion criteria	Adults ≥18 years; with confirmed prior SARS-CoV-2 infection; persistent symptoms consistent with PASC; symptoms lasting ≥3 months post-infection; weight greater than 40 kg; estimated glomerular filtration rate of 60 mL/min or higher.
Exclusion criteria	Pregnancy or breastfeeding; severe liver disease; SARS-CoV-2 infection, and use of SARS-CoV-2-specific treatment within 30 days of randomization; SARS-CoV-2 vaccination within 28 days, or other vaccine within 14 days of randomization, or medications that interact with study drug.
Intervention Participants (n) Drop-outs (n)	Nirmatrelvir-ritonavir group: 300 mg nirmatrelvir + 100 mg ritonavir twice daily for 15 days. n=102 n=4
Control Participants (n)	Placebo group: matching placebo regimen + 100 mg ritonavir twice daily for 15 days. n=53

Drop-outs (n)	n=4
Follow up time points	Baseline, and thereafter at several time points until 10 weeks post-randomization.
Outcomes Measured	Primary: Change in pooled PASC symptom severity scores (fatigue, brain fog, body aches, cardiovascular symptoms, shortness of breath, gastro-intestinal symptoms) at 10 weeks measured using Likert scales from 0 to 3. Secondary: Symptom severity at different time points, symptom burden and relief, patient global measures, Patient-Reported Outcomes Measurement Information System (PROMIS) measures, sit-to-stand test change from baseline, PGIS and PGIC. Safety: adverse events.
Results	Primary outcome: Change in pooled PASC symptom severity scores at 10 weeks: No statistically significant difference between groups at 10 weeks, adjusted for baseline severity. Secondary outcomes: Symptom severity at different time points during 15 weeks: no consistent patterns to distinguish NMV/r from PBO/r groups. Symptom burden and relief: no statistically significant differences in proportion of participants experiencing relief at 5, 10, and 15 weeks; alleviation at 10 weeks; or time to relief of each core symptom and the most bothersome symptom. Patient global measures and PROMIS measures: Changes from baseline in PGIS and PGIC scores at 2, 5, 10, and 15 weeks and PROMIS scales for physical function, fatigue, dyspnea, and cognitive abilities showed no statistically significant between-group difference at 10 week.

	Sit-to-stand test change from baseline: no significant between-group differences at 10 weeks. Adverse events: rates were similar in NMV/r and PBO/r groups and mostly of low grade.
Limitations Noted	Single-center; modest sample size; follow-up limited to 10 weeks; heterogeneous symptom presentation; lack of biomarker data; findings may not generalize to severe or hospitalized COVID-19 cases.
Risk of bias	Low

Gupta 2022

Author Reference	Gupta et al. [11]
Year	2022
Country	USA
Study Design	Phase 2 randomized clinical trial (triple-blinded, placebo-controlled).
Setting	Conducted virtually; participants from Missouri and Illinois, USA.
Population	51 adults (mean age 46 ± 13 years; 71% female) with chronic olfactory dysfunction 3–12 months after suspected COVID-19 infection.
Inclusion criteria	Adults with olfactory dysfunction 3–12 months after suspected COVID-19; University of Pennsylvania Smell Identification Test (UPSIT) ≤33 (men) or ≤34 (women).
Exclusion criteria	History of olfactory dysfunction before COVID-19; nasal polyps; prior sinonasal or skull base surgery; neurodegenerative disease; prior seizures; arrhythmia; pregnancy; breastfeeding; current theophylline or

	methylxanthine use; allergy to theophylline; other contraindications.
Intervention Participants (n) Drop-outs (n)	Treatment group: Saline nasal irrigation (SNI) with 400 mg theophylline twice daily for 6 weeks. n=26 n=4
Control Participants (n) Drop-outs (n)	Control group: SNI with placebo (lactose powder) twice daily for 6 weeks. n=25 n=2
Follow up time points	Baseline, 3 weeks, and 6 weeks assessments.
Outcomes Measured	Primary: Clinical Global Impression-Improvement (CGI-I) scale responders (≥slightly better). Secondary: UPSIT score changes; Questionnaire for Olfactory Disorders (QOD) Adverse effects.
Results	Primary: CGI-I scale responders (≥slightly better): 13 (59%) participants in the theophylline arm compared with 10 (43%) in the placebo arm (absolute difference between groups, 15.6%; 95%CI, −13.2% to 44.5%). Secondary: UPSIT score changes: Not statistically significantly different between the 2 study arms.

	QOD: Change in score on each of the 4 QOL assessments related to smell loss was not different between the study arms. Adverse effects: Similar between groups at 6 weeks, no severe adverse effects.
Limitations Noted	Virtual design limited physical examinations; small sample size; many participants correctly guessed placebo; short follow-up (6 weeks); did not collect vaccination status; inconclusive efficacy findings.
Risk of bias	Low

Guttoso 2024

Author Reference	Guttuso et al. [12]
Year	2024
Country	USA
Study Design	Randomized clinical trial (double-blind, placebo-controlled) with subsequent open-label dose-finding study.
Setting	University at Buffalo, New York, USA (neurology clinic).
Population	52 participants (58% male; mean age 58.5 years) with post–COVID-19 condition (PCC) fatigue or cognitive dysfunction >4 weeks post infection; all self-reported positive COVID-19 test; symptoms persisted >6 months for ~10%.
Inclusion criteria	Positive COVID-19 test; bothersome fatigue or cognitive dysfunction >4 weeks post infection; FSS-7 or BFSS score ≥28; BDI-II score <29; no conditions known to cause fatigue or cognitive dysfunction prior to covid-infection; no tobacco/THC use >6 months; not pregnant or nursing.
Exclusion criteria	History of lithium use; psychoactive/steroid medication change within 30 days; fibromyalgia, chronic fatigue syndrome, rheumatoid arthritis, or other fatigue/cognitive dysfunction conditions; applying for disability for PCC.
Intervention Participants (n) Drop-outs (n)	Lithium aspartate 10–15 mg/day for 3 weeks. n=26 n=2 (Data from open-label phase and dose-finding phase not extracted by SBU).
Control	Placebo for 3 weeks

Participants (n) Drop-outs (n)	n=26 n=0
Follow up time points	Baseline, 3 weeks.
Outcomes Measured	Primary: Change in combined FSS-7 and BFSS scores. Secondary: Insomnia Severity Index, Generalized Anxiety Disorder Scale-2, Beck Depression Inventory-II, Short-Form-12 Health Survey (SF-12) physical/mental scores.
Results	Between-group difference at 3 weeks (95% CI): Primary: Change in combined FSS-7 and BFSS scores: not statistically significantly different between groups; -3.6 (-16.6 to 9.5). Secondary: Insomnia Severity Index: not statistically significantly different between groups; -1.6 (-5.5 to 2.3). Generalized Anxiety Disorder Scale-2: not statistically significantly different between groups; 0.6 (-0.5 to 1.8). BDI-II: not statistically significantly different between groups; 0.4 (-3.5 to 4.2). SF-12, Physical Component Score: not statistically significantly different between groups; 0.9 (-4.8 to 6.6). SF-12, Mental Component Score: not statistically significantly different between groups; 2.2 (-3.3 to 7.6).

	Additional outcomes reported.
Limitations Noted	Small sample size; short follow-up; lack of biomarker assessment; preliminary nature of findings; findings not definitive on efficacy of higher doses.
Risk of bias	Low

He 2024

Author Reference	He et al. [13]
Year	2024
Country	China
Study Design	Pilot randomized controlled trial (parallel, prospective).
Setting	Renmin Hospital of Wuhan University, Department of Respiratory and Critical Care Medicine, Wuhan, China.
Population	73 adults with post-acute sequelae of COVID-19 (PASC) after Omicron infection; median age ~68–71 years; persistent symptoms ≥20 weeks; mixed comorbidities (hypertension, diabetes, CHD, etc.).
Inclusion criteria	Adults aged 18–80 years with confirmed omicron SARS-CoV-2 infection (Dec 2022–Jan 2023); consistent with NICE definition of PASC; stable medical condition; no significant changes in treatment over the last three months.
Exclusion criteria	Acute SARS-CoV-2 infection within 4 weeks; pregnancy; menstruating; acute physical disease (e.g., myocardial infarction, stroke); severe liver dysfunction; bleeding disorders; allergy to anticoagulants; epilepsy; hemochromatosis; toxic diffuse goiter; severe anemia (<90 g/L hemoglobin).
Intervention	O3-MAH group: Major ozone autohemotherapy daily for 7 days + conventional treatment.

Participants (n) Drop-outs (n)	n=38 n=3
Control Participants (n) Drop-outs (n)	Conventional group: Conventional therapy (inhaled bronchodilators, oral antitussives/mucolytics, nebulized corticosteroids/anticholinergics) for 7 days. n=39 n=1
Follow up time points	Baseline and post-treatment (7 days) assessments; no long-term follow-up
Outcomes Measured	Primary: Symptom score (sore throat, cough, expectoration, nasal congestion and/or runny nose, shortness of breath, chest tightness, chest pain, palpitations, headache, fatigue, insomnia, loss of smell and taste, and loss of appetite), 6-minute walk distance (6MWD), lung function: Forced vital capacity (FVC), Forced expiratory volume in one second (FEV1), tidal volume (VT).
Results	Between group differences at end-of-treatment (at 7 days): Symptom score: statistically significant improvement in favor of intervention group; Md (IQR) 3 (2, 4) vs 4 (3, 7), p = 0.0478. 6MWD, meters: not statistically significantly different between groups, p = 0.2633. 6MWD, % of expected distance: statistically significantly better in the O3-MAH group; Md (IQR) 95.97 (93.04, 101.63) vs 89.65 (80.50, 98.17), p = 0.0032.

	Lung function: FVC, L/min: not statistically significantly different between groups, p = 0.7400. FEV1, L/min: not statistically significantly different between groups, p = 0.9013 VT, L: statistically significantly better in the O3-MAH group; Md (IQR) 0.77 (0.63, 0.98) vs 0.61 (0.415, 0.84), p = 0.0374. Additional outcomes reported. No participant indicated treatment-related symptoms nor adverse events.
Limitations Noted	Per protocol-analysis; single-center; open-label (no blinding); short follow-up; small sample size; variable baseline inflammation; lack of stratified analysis by severity; no long-term outcomes.
Risk of bias	Moderate

Kaczmarczyk 2024

Author Reference	Kaczmarczyk et al. [14]
Year	2024
Country	Poland
Study Design	Randomized controlled trial (parallel, intervention vs. control).
Setting	Józef Piłsudski University of Physical Education in Warsaw, Poland.
Population	51 older adults (≥65 years). Mean age ~69–75 years. Both sexes. Post-COVID survivors (average 9 months since onset). 92% vaccinated. Infection described as mild for 33%, moderate for 51%, severe for 10%, very severe for 6%.
Inclusion criteria	≥65 years old; positive RT-PCR or antibody test for SARS-CoV-2 in last 3–12 months; at least one post-COVID symptom (e.g., fatigue, weakness, dizziness, headache,

	memory issues, exercise intolerance, depression); medically screened for exacerbations of post-exercise symptoms, able to participate in resistance training.
Exclusion criteria	<65 years; active cardiac disease; oxygen desaturation <95% for more than 1 min; autonomic dysfunction (orthostatic intolerance); serious health conditions (e.g., cancer).
Interventions	Resistance training program: twice weekly, 60 min sessions, 8 weeks. Exercises: incline bench press, 45° leg press, latissimus pull-down, trunk crunch, T-Bar row, leg extension, leg curl. Intensity: 70% of 1RM, 3 sets × 12 reps. Warm-up 15 min.
Participants (n)	n=28
Drop-outs (n)	n=2
Control	Continued usual physical activity without modifications.
Participants (n)	n=23
Drop-outs (n)	n=3
Follow up time points	Baseline and post-intervention (8 weeks) assessments
Outcomes Measured	Muscle strength (isometric, isokinetic); Functional performance (Timed Up and Go, Chair Stand Tests: 5STS, CS-30); Self-reported post-COVID symptoms.
Results	GROUP (control, intervention) x TESTING SESSION (before, after):
	TUG (seconds)
	F (1,42) = 3.06
	p = 0.0876

	$\eta^2 = 0.068$ Chair test 5STS (seconds) F (1,42) = 8.49 p = 0.0057 $\eta^2 = 0.168$ Chair test CS-30 (No. of repetitions) Z = 4.65 p = 0.0001 R = 0.806 Additionally, muscle strength reported in several tests. Percentage of post-COVID symptoms reported for intervention group.
Limitations Noted	Small sample size; intervention group already high functioning; no systematic tracking of symptoms in control group; reliance on gym equipment may limit generalizability. Short intervention duration; limited diet control; lack of biochemical data; small sample size; no non-COVID control group; generalizability limited to elderly adults
Risk of bias	Moderate

Kaddoussi 2024

Author Reference	Kaddoussi et al. [15]
Year	2024
Country	Tunisia

Study Design	Randomized controlled trial (single-blinded).
Setting	Outpatient departments of pulmonology and physical medicine & rehabilitation, Fattouma Bourguiba Hospital, Monastir, Tunisia.
Population	36 adult long-COVID-19 patients (LC19Ps) with persistent dyspnoea ≥3 months post-diagnosis; mean age 52–53 years; mix of sexes; comorbidities include diabetes, hypertension; excluded active smokers; varying lung injury extents on CT.
Inclusion criteria	Confirmed COVID-19; age >18; persistent dyspnoea ≥3 months post-diagnosis; mMRC dyspnoea score ≥2.
Exclusion criteria	Pre-existing chronic lung diseases (asthma, COPD, lung cancer); moderate/advanced heart failure; mobility-limiting conditions; active cigarette/narghile smokers; contraindications to 6MWT or spirometry; missed sessions or evaluations.
Intervention Participants (n) Drop-outs (n)	Ambulatory cardiopulmonary rehabilitation program (CPRP) – 18 sessions over 6 weeks including warm-up, aerobic treadmill training, resistance exercises, respiratory exercises, therapeutic education. n=24 n=4
Control Participants (n) Drop-outs (n)	Usual care/sedentary activity n=12 n=2
Follow up time points	Baseline (pre-CPRP) and post-CPRP (6 weeks); additional 2-week evaluation phase pre- and post-intervention.
Outcomes Measured	Primary: 6-minute walk distance (6MWD).

	Secondary: Dyspnoea (Borg, mMRC), spirometry (FEV1, FVC), heart rate (rest and end), SpO2, 6-minute walk work (6MWW). Minimal clinically important difference (MCID) defined as 30 m for 6MWD and 1 point for mMRC.
Results	Post-CPRP, I: n=20, C: n=10. 6MWD (m): IG significantly increased by 168 ± 99 m vs. CG's 5 ± 45 m (exceeded MCID of 30 m). Dyspnoea reduction: IG improved mMRC by -1.5 ± 0.8 (MCID: 1), CG by -0.1 ± 0.3. IG improved Borg by -3.5 ± 2.0, CG by -1.3 ± 1.5. Resting heart rate: IG decreased by -9 ± 9 bpm, CG change was 1 ± 7 bpm. Spirometry: Small improvements in IG (FEV1, FVC), but no statistical or clinical difference compared to CG. Safety: No patients stopped during 6MWT; no side effects noted. Abnormal 6MWD percentage: IG decreased from 100% to 75%, CG unchanged at 80%.
Limitations Noted	Single center; small sample size; short follow-up (6 weeks); no post-6MWT blood pressure or recovery SpO2 measured; no bronchodilator tests; limited equipment (no plethysmography or diffusion capacity tests); no waist circumference data; results may not generalize to other populations.
Risk of bias	Moderate

Khodabahkshian 2025

Author Reference	Khodabakhshian et al. [16]
Year	2025
Country	Iran

Study Design	Randomized controlled trial (double-blind).
Setting	Kashan University of Medical Sciences, Kashan, Iran.
Population	52 adults with persistent fatigue ≥6 weeks after acute COVID-19;; mean age ~37 years; majority female (approx. 86% in intervention group, 64% in sham group).
Inclusion criteria	Age 18–65; Iranian nationality; persistent fatigue (Chalder Fatigue Scale >4); PCR confirmed COVID-19 ≥6 weeks prior; physician-approved treatment completion.
Exclusion criteria	Acute severe disease; chronic diseases (anemia, MS, cancer, psychiatric disorders); pregnancy or breastfeeding; BMI >40 kg/m²; COVID-19 complications (e.g., thromboembolism); mechanical ventilation during acute COVID-19; auricular health problems; acupressure/acupuncture in prior 3 months; medication/substance abuse; complementary therapy use.
Intervention Participants (n) Drop-outs (n)	Intervention group: Auriculotherapy with Vaccaria seeds on six fatigue-related ear points for 4 weeks, pressed twice daily (60 presses/session, 5 days/week). Weekly replacements of seeds/tapes. n=26 n=4
Control Participants (n) Drop-outs (n)	Sham group: Adhesive tape without seeds on same points; no pressing. Weekly replacements of seeds/tapes. n=26 n=4
Follow up time points	Baseline (T0), immediately post-intervention (T1, 4 weeks), and 4 weeks after intervention (T2, 8 weeks total) assessments using Chalder Fatigue Scale.

Outcomes Measured	Primary: Fatigue score (Chalder Fatigue Scale; CFS). Secondary: None specified; adverse events (itching, allergic reactions) monitored.
Results	Adjusted (financial status and history of hospitalization due to COVID-19) ITT-results: Fatique score (CFS): Repeated-measures ANOVA revealed a significant time-group interaction for fatigue [F (2,50) = 6.978; p= 0.008].
Limitations Noted	Single center; modest sample size; high proportion of female/educated participants (generalizability limited); possible placebo effects from sham adhesive tapes; lack of biomarker confirmation; short follow-up; potential misclassification due to PCR sensitivity.
Risk of bias	Moderate

Leon-Herrera 2024

Author Reference	León-Herrera et al. [17]
Year	2024
Country	Spain
Study Design	Randomized clinical trial (blind, parallel groups).
Setting	Spanish Long-COVID associations; online multimodal rehabilitation program with videoconferences and Moodle platform.
Population	134 participants (mean age ~49 years; 84% female) with persistent symptoms ≥3 months post-COVID; members of Spanish Long-COVID collectives.
Inclusion criteria	Adults aged 18–80; persistent COVID symptoms ≥3 months; member of Spanish Long-COVID associations; no alternative diagnosis.

Exclusion criteria	Serious uncontrolled medical conditions; concurrent rehabilitation or psychotherapy; participation in another trial within 6 months; pregnancy/lactation; suicide risk; significant medical, psychological, or social issues preventing participation.
Intervention	Usual care plus online multimodal program (8 weekly 1.5h sessions via videoconference + Moodle resources) covering physical activity, respiratory rehabilitation, cognitive rehabilitation, diet, sleep hygiene, emotional management, meditation; community participation.
Participants (n)	n=67
Drop-outs (n)	n=5
Control	Usual care
Participants (n)	n=67
Drop-outs (n)	n=5
Follow up time points	Baseline and 3 months post-intervention assessments.
Outcomes Measured	Primary: Quality of life (SF-36 physical and mental health scores). Secondary: persistent symptoms, cognitive function (MoCA), lower limb strength (Sit-to-Stand), anxiety/depression (HADS), sleep (ISI), self-efficacy, health literacy, patient activation.
Results	Per protocol-analysis at 3 months post-intervention, I: n=62, C: n=62, mean change from baseline (SD):
	SF-36 Physical Health
	I: 1 .97 (8.77) vs C: 1 .38 (6 83), p = 0.678

	SF-35 Mental Health I: 1 .98 (8.87) vs C: -1 .26 (8 99), p= 0.046 Number of persistent symptoms I: -0.73 (4.41) vs C: -0.27 (31 7), p = 0.514 MoCA I: 0.53 (2.26) vs C: 0.42 (2.83), p= 0.807 Sit-to-Stand Test I: 0.58 (2.76) vs C: 0.29 (2.98), p = 0.094 HADS I: -1 .87 {6.24) vs C: -0. 1 0 {5.59), p = 0.098 ISI I: -1 1 9 (5.82) vs C: -0.52 {5.20), p = 0.496 Self-efficacy I: -0.85 (8.85) vs C: 0.77 (6.19), p = 0.953
Limitations Noted	Per protocol-analysis; participants unblinded; differences in baseline symptoms; adherence variability; predominantly female sample; reinfections/relapses during program; short-term follow-up (3 months).
Risk of bias	Moderate

Lukkunaprasit 2024

Author Reference	Lukkunaprasit et al. [18]
Year	2024
Country	Thailand
Study Design	Randomized controlled trial (double-blind, placebo-controlled).
Setting	College of Pharmacy, Rangsit University, Thailand.
Population	66 participants (mean age ~41 years; majority female) with persistent long COVID symptoms ≥4 weeks post-infection; most had mild initial COVID-19 illness.
Inclusion criteria	Thai adults ≥20 years; confirmed COVID-19 (antigen or PCR test) ≥4 weeks prior; at least one long COVID symptom verified by physician; willing to complete study procedures.
Exclusion criteria	Current/suspected pneumonitis, chronic obstructive pulmonary disease, chronic lung diseases, chronic renal disease, cardiovascular diseases, cerebrovascular diseases, congenital heart diseases, psychotic disorders, hepatitits, cirrhosis, immunodeficiency disorders, positive THC test, pregnancy/breastfeeding, warfarin or benzodiazepine use, hypersensitivity to intervention, participation in other trials, other conditions interfering with participation.
Intervention Participants (n) Drop-outs (n)	Clears-belong Plus (CPE): combined plant extract 4500 mg/day (1500 mg 3 times daily) (Citrus aurantifolia, Tiliacora triandra, Cannabis sativa, Alpinia galanga, Piper nigrum) for 7 days. n=33 n=2
Control	Identical placebo

Participants (n) Drop-outs (n)	n=33 n=11
Follow up time points	Post-intervention (day 8), and safety follow-up calls up to day 14.
Outcomes Measured	Primary: Change in CRP levels and total symptom score (0–57 scale): not reported by SBU. Secondary: Full recovery (symptom score=0), improvement in symptoms, HRQOL (EQ-5D-5L utility and VAS scores), adverse events.
Results	Post treatment (day 8): Total symptom score, median (IQR) CPE: 5 (3, 8) Placebo: 8 (3, 11) EQ-5D-5L, utility score, median (IQR) CPE: 0.96 (0.94, 1.00) Placebo: 1.00 (0.96, 1.00) EQ-5D-5L, VAS score, median (IQR) CPE: 90 (85, 95) Placebo: 95 (85, 95) Any moderate to severe symptoms

	RR (95% CI): 0.57 (0.35 to 0.91) Moderate to severe fatigue RR (95 % CI): 0.25 (0.08 to 0.81) Moderate to severe PEM RR (95% CI): 0.35 (0.16 to 0.78) Adverse events (n) CPE: 31 Placebo: 33
Limitations Noted	Small sample size; short duration (7 days); new unvalidated symptom questionnaire; high placebo dropout (unblinding risk); low adherence rates; exclusion of many comorbidities limits generalizability.
Risk of bias	Moderate

Maritescu 2024

Author Reference	Maritescu et al. [19]
Year	2024
Country	Romania
Study Design	Randomized controlled trial (single-masked, outcome assessor blinded).
Setting	Pulmonary Rehabilitation Center, Clinical Hospital of Infectious Diseases and Pulmonology ‘Victor Babes’, Timisoara, Romania.

Population	61 adults aged 54–74 years with long-term COVID-19 symptoms (moderate to severe dyspnea and fatigue) persisting ≥3 months post-infection.
Inclusion criteria	Confirmed COVID-19 via RT-qPCR or antibody test; moderate/severe dyspnea and fatigue lasting ≥3 months post-infection; age 18–75; stable medical condition; no recent exacerbations or hospitalizations in past 3 months.
Exclusion criteria	Severe comorbid conditions (heart disease, stroke, neurodegenerative diseases, acute illnesses); major surgery or hospitalization within past 6 months; severe psychiatric/cognitive disorders; active respiratory infections; immunocompromised status; severe mobility impairments; high alcohol or substance abuse.
Intervention Participants (n) Drop-outs (n)	21-day pulmonary rehabilitation (aerobic, strength, breathing exercises) + daily 20-min progressive muscle relaxation sessions. n=35 n=4
Control Participants (n) Drop-outs (n)	21-day pulmonary rehabilitation (aerobic, strength, breathing exercises). n=35 n=5
Outcomes Measured	Primary: Mental health (GHQ-12, PHQ-9, GAD-7) and sleep quality (PSQI). Secondary: Lung function (FVC, FEV1), exercise capacity (6MWT).

Results	The group receiving PR+PMR showed greater improvement in mental health (GHQ-12), depression (PHQ-9), anxiety (GAD-7), and sleep quality (PSQI) compared to PR alone ($p<0.0001$ for all comparisons). No significant difference in exercise capacity improvement between groups ($p=0.1711$).
Limitations Noted	Per protocol-analysis; single-center; small sample size (61 participants); short intervention (21 days); older adult population limits generalizability; no long-term follow-up to assess sustainability of improvements
Risk of bias	Moderate

Nerli 2024

Author Reference	Nerli et al. [20]
Year	2024
Country	Norway
Study Design	Randomized clinical trial (pragmatic, parallel group).
Setting	Single referral center in South-Eastern Norway Regional Health Authority.
Population	314 patients with mild to moderate post-COVID-19 condition; mean age 43 years; 72% female; symptoms ≥3 months; functional disability interrupting normal activities.

Inclusion criteria	Age ≥16; confirmed COVID-19 (PCR or antigen); persistent symptoms ≥3 months; functional disability interrupting normal activities.
Exclusion criteria	Other chronic illness explaining symptoms; sustained organ damage (heart, lung, neurological disorders); bedridden; insufficient Norwegian language skills.
Intervention Participants (n) Dropouts (n)	Intervention group (n=157): Brief outpatient rehabilitation program (2–8 encounters, 2–6 weeks apart) based on Cognitive Activation Theory of Stress (CATS); physicians and physiotherapists trained in cognitive and behavioral approaches. n=157 n=55
Control Participants (n) Dropouts (n)	Care as usual n=157 n=32
Follow up time points	Baseline (T0), post-intervention (T1), and 12 months after inclusion (T2).
Outcomes Measured	Primary: Physical function (SF-36 Physical Function Subscale). Secondary: SF-36 subscales (vitality, general health, social function, etc.), return to work self-efficacy, fatigue, post exertional malaise, breathlessness, cognitive difficulties, sleep problems, anxiety, depression, smell/taste abnormalities. Safety outcomes: healthcare contacts, hospital admissions, novel diseases, worsening symptoms, work ability, suicidality.
Results	ITT-analysis with multiple imputation of missing values. Results adjusted for baseline values of each effectiveness end point.

	SF-36 subscores, T2 (12 months after inclusion), MD (95% CI): Physical function: 9.0 (4.0 to 13.9) Role limitations due to physical problems: 14.9 (3.6 to 26.2) Bodily pain: 2.4 (−1.0 to 5.8) General health: 7.6 (1.2 to 13.9) Vitality: 7.6 (2.3 to 13.0) Social functioning: 14.0 (7.2 to 20.8) Role limitations due to emotional problems: 17.4 (4.4 to 30.4) Mental health: 6.6 (3.3 to 9.9) Return to work self-efficacy, T2, MD (95% CI): 0.4 (0.1 to 0.7). Symptoms, T2, MD (95% CI): Fatigue: −2.4 (−4.2 to −0.7) Post-exertional malaise: −12.4 (−19.8 to −5.1) Breathlessness: −0.4 (−0.6 to −0.2) Cognitive difficulties: −0.3 (−0.5 to −0.1) Sleep problems: 4.8 (2.3 to 7.4) Anxiety symptoms: −0.9 (−1.6 to −0.2) Depressive symptoms: −1.2 (−1.9 to −0.5) Smell and/or taste abnormalities: −0.1 (−0.4 to 0.2) Results at T1 (post intervention) also reported in study

	For SF-36, physical function subscore, a difference of 10 points was considered clinically significant.
Limitations Noted	Single-center design; lack of blinding (possible placebo effects); moderately impaired, mostly nonhospitalized participants (limits generalizability); attention imbalance between groups; no sham intervention; patient-reported outcomes only; potential missing data bias
Risk of bias	Moderate

Rana 2025

Author Reference	Rana et al. [21]
Year	2025
Country	India
Study Design	Double-blind randomized placebo-controlled feasibility trial (two parallel arms).
Setting	D. N. De Homoeopathic Medical College & Hospital, Kolkata, West Bengal, India.
Population	60 adults (aged 18–65) with post-COVID-19 conditions (symptoms ≥3 months); 76.7% female in IHMP group, 56.7% in control group.
Inclusion criteria	Confirmed SARS-CoV-2 infection; ≥3 months from onset; symptoms lasting ≥2 months; literate adults; able to consent.
Exclusion criteria	Pneumonia, SpO2 <95%, abnormal labs (liver enzymes, lipid profile, urea, creatinine, blood sugar), hypertension ≥140/90 or hypotension <90/60, chronic diseases (uncontrolled diabetes, heart, liver, kidney disease), malignancy, psychiatric illness, COPD/asthma, concurrent other treatments, pregnancy/lactation, substance abuse, prior homeopathy within 6 months, concurrent trial participation.
Intervention	IHMP group: Individualized homeopathic medicines (Natrum muriaticum, Pulsatilla nigricans, Rhus toxicodendron, Calcarea carbonica, etc.) in centesimal potencies (6c, 30c,

	200c, 1000c) plus concomitant care for 3 months. Standard non-pharmacological advice.
Participants (n) Drop-outs (n)	n=30 n=1
Control	Placebo group: Identical-looking placebo globules plus concomitant care for 3 months. Standard non-pharmacological advice.
Participants (n) Drop-outs (n)	n=30 n=2
Follow up time points	Baseline, monthly assessments up to 3 months.
Outcomes Measured	Primary: Post-COVID-19 symptoms checklist score. Secondary: Measure Yourself Medical Outcomes Profile v2 (MYMOP-2) scores (symptom 1, symptom 2, activity difficulty, well-being). Feasibility metrics: recruitment (34%), retention (95%), attrition (5%).
Results	ITT analysis. Missing data imputed through linear regression. Post COVID-19 symptom checklist scores, MD (SE) Total symptom score: -4.2 (0.4). MYMOP-2 scores Symptom 1: -2.4 (0.3) Symptom 2: -.24 (0.4)

	Difficulty in activity: -2.3 (0.3) Feeling of well-being: -1.8 (0.3) Profile score: -2.2 (0.3) Results are also reported after 1 and 2 months.
Limitations Noted	Feasibility design; small sample size; short trial duration (3 months); single center; use of rescue remedies during unrelated acute events (potential confounding); predominance of female participants; no long-term follow-up.
Risk of bias	Moderate

Redel 2024

Author Reference	Redel et al. [22]
Year	2024
Country	The Netherlands
Study Design	Randomized, double-blind, placebo-controlled trial.
Setting	Franciscus Gasthuis & Vlietland Hospital, Rotterdam, Netherlands.
Population	72 adults aged 18–70 years with long COVID (persistent symptoms ≥3 months) within 12 months of SARS-CoV-2 infection; median age ~48 years; 62.5% female.
Inclusion criteria	PCR-confirmed SARS-CoV-2 infection; at least two long COVID symptoms per WHO criteria; symptoms <1 year; aged 18–70.
Exclusion criteria	ICU admission for COVID-19; abnormal chest radiograph or pulmonary function test; current acute COVID-19; systemic immunological disorders; psychiatric disorders; use of immune-modulatory drugs; pregnancy or lactation; milk allergy.

Intervention Participants (n) Dropouts (n)	Lactoferrin 1200 mg/day (600 mg twice daily) orally for 6 weeks + usual care (physiotherapy/psychological support as needed). n=36 n=4
Control Participants (n) Dropouts (n)	Identical appearance placebo capsules twice daily for 6 weeks + usual care. n=36 n=3
Follow up time points	Baseline (T0), 6 weeks (T6), and 12 weeks (T12) post-randomization assessments.
Outcomes Measured	Primary: Fatigue (Fatigue Assessment Scale). Secondary: Anxiety and depression (HADS), cognitive failure (CFQ), muscle strength (handgrip, sit-to-stand), laboratory parameters (ferritin, transferrin saturation, CK, etc.).
Results	No significant difference in fatigue between lactoferrin and placebo at 6 or 12 weeks. No differences between groups on secondary outcomes at 6 or 12 weeks. Side effects mild and similar between groups.
Limitations Noted	Single-center; relatively small sample size; concurrent other therapies (physiotherapy, occupational therapy) may confound results; short follow-up; potential placebo/Hawthorne effect; no pre-long-COVID baseline data; uncertain dose/frequency adequacy.
Risk of bias	Low

Rodriguez-Moran 2024

Author Reference	Rodríguez-Morán et al. [23]

Year	2024
Country	Mexico
Study Design	Open label randomized controlled clinical trial.
Setting	Mexican Social Security Institute, Durango, Mexico
Population	60 adults (mean age 52.8 ± 12.6 years) with hypomagnesemia, vitamin D deficiency, and mild-to-moderate depression related to long-COVID; confirmed COVID-19 diagnosis via PCR; symptoms persisting ≥12 weeks.
Inclusion criteria	Adults >30 years; confirmed COVID-19 (PCR); hypomagnesemia (sMg<1.8 mg/dL); vitamin D deficiency (25-OH vit D <30 ng/mL); mild-to-moderate depression (BDI 11-30) persisting ≥12 weeks.
Exclusion criteria	Pregnancy; use of antidepressants or magnesium/vitamin D supplements in past 90 days.
Intervention Participants (n) Dropouts (n)	Magnesium chloride 1300 mg (382 mg elemental magnesium) + Vitamin D 4000 IU daily for 4 months. Supplements administered post-breakfast. n=30 n=0
Control Participants (n) Dropouts (n)	Vitamin D 4000 IU daily for 4 months. Supplements administered post-breakfast. n=30 n=1
Follow up time points	Baseline and 4 months post-intervention assessments (BDI, serum magnesium, vitamin D, metabolic parameters).
Outcomes Measured	Primary: Beck Depression Inventory (BDI) score (improvement defined as BDI <11). Secondary: Serum

	magnesium and vitamin D levels; metabolic parameters (glucose, triglycerides, HDL-c). Adverse events (mild gastrointestinal symptoms) monitored.
Results	Beck Depression Inventory (BDI) scores (assumed to report mean ± SD). I: 9.2 ± 7.5 C: 21.6 ± 9.1 p: 0.006 • Adverse events (mild, no withdrawals), n. I: 6 C: 3
Limitations Noted	Per protocol-analysis; open-label design; lack of placebo control; small sample size; no pre-COVID baseline BDI scores; conducted at single center.
Risk of bias	Moderate

Sanchez-Mila 2024

Author Reference	Sanchez Milá et al. [24]
Year	2024
Country	Spain
Study Design	Randomized clinical trial (controlled experimental study).
Setting	Catholic University of Avila, Spain (NEUMUSK Group Research, Department of Physiotherapy).
Population	200 university students with post-COVID-19 symptoms >5 months; aged 18–45 years; complaints of dyspnea, fatigue, and loss/reduction of smell and taste.

Inclusion criteria	Medically diagnosed COVID-19 via PCR; >5 months post-infection; symptoms of dyspnea; loss or decrease of smell and taste; age 18–45 years.
Exclusion criteria	Severe exercise intolerance; ischemia during low-intensity exercise; severe pulmonary hypertension; severe COVID-19 symptoms; recent cardiovascular events; cancer; muscular or severe neurological diseases.
Intervention Participants (n) Dropouts (n)	31-day home-based rehabilitation program combining inspiratory training (PowerBreathe Plus device (30 breaths/day, 5 mins), aerobic walking exercise for 40 mins/day at 60-75% max heart rate, and olfactory/gustatory training with specified odours and tastes daily (onion, detergent, sugar, salt, orange juice, coffee). n=105 n=5
Control Participants (n) Dropouts (n)	No therapy for 31 days. n=104 n=4
Follow up time points	Baseline (day 1), mid-treatment (day 2 for dyspnea scores), and post-treatment (day 31) assessments.
Outcomes Measured	Primary: Respiratory outcomes (FVC, FEV1/FVC ratio, PImax); dyspnea scores (modified Borg scale, MMRC). Secondary: Neurological outcomes (Singapore Smell and Taste Questionnaire scores for smell and taste).
Results	Intervention group showed significant improvement compared to control in: - FVC ($p<.001$)

	- FEV1/FVC ratio (p<0.01) - Peak Inspiratory Pressure (p<0.01) - Dyspnea MBS and MMRC scales (p<0.01) - Olfactory and gustatory scores in SSTQ (p<0.01) No significant improvement in FEV1 Effect sizes were medium to large.
Limitations Noted	Single-center; limited to university-aged adults (18–45); no long-term follow-up; lack of pre-COVID baseline data; reliance on self-reported olfactory/gustatory scores; non-supervised home exercises (potential adherence issues).
Risk of bias	Moderate

Tryfonos 2024

Author Reference	Tryfonos et al. [25]
Year	2024
Country	Sweden
Study Design	Randomized crossover clinical trial.
Setting	Karolinska University Hospital and Karolinska Institute, Sweden.
Population	31 adults with PCC; mean age ~47 years; 76% female; persistent symptoms ≥3 months post-SARS-CoV-2 infection; no prior hospitalization; no significant comorbidities 31 healthy controls were also recruited.
Inclusion criteria	Age 18–64; laboratory-confirmed SARS-CoV-2 infection; persistent post exertional malaise ≥3 months; no prior hospitalization; no history of cardiovascular/respiratory disease or somatic symptom disorder; symptom onset after March 2020.

Exclusion criteria	Presence of chronic illnesses explaining symptoms; organ damage; insufficient Norwegian language skills (not applicable here); pregnancy not specified.
Intervention Participants (n) Dropouts (n)	High intensity interval training (HIIT). 26 to 30 (order of type of training not specified) 0 to 4 (not specified at which training session participants discontinued).
Intervention Participants (n) Dropouts (n)	Moderate-intensity continuous training (MICT). 26 to 30 (order of type of training not specified). 0 to 4 (not specified at which training session participants discontinued).
Intervention Participants (n) Dropouts (n)	Strength training (ST). 26 to 30 (order of type of training not specified). 0 to 4 (not specified at which training session participants discontinued).
Follow up time points	Baseline, immediately after exercise, and 48 hours post-exercise for each intervention.
Outcomes Measured	Post exertional symptoms as assessed by VAS for 10 symptoms (fatigue, muscle pain, joint pain, fever, chills, lymph node discomfort, sore throat, headache, memory, and concentration); Multidimensional Fatigue Inventory; Profile of Mood States; Somatic and Psychological Health Report.
Results	Results at 48 hours post-exercise: Fatigue VAS 0-10, median (IQR) HIIT:6.0 (4.0 to 8.0)

	MICT: 4.5 (2.8 to 7.0) ST: 5.0 (4.0 to 7.0) MFI Total, median (IQR) HIIT: 66.0 (56.5, 76.0) MICT: 66.5 (57.2, 73.8) ST: 64.0 (54.5, 70.0) POMS Total Mood Disturbance, median (IQR) HITT: 32.0 (13.5, 49.0) MICT: 33.5 (18.5, 52.8) ST: 28.0 (16.0, 45.5) SPHERE SOMA, median (IQR) HIIT: 6.5 (4.2, 10.0) MICT: 6.5 (4.2, 9.0) ST: 6.0 (4.0, 9.8) SPHERE PHYSH, median (IQR) HIIT: 1.0 (0.0, 2.8) MICT: 1.0 (0.0, 3.0) ST: 0.0 (0.0, 2.0) Subscales and other results are also reported.
Limitations Noted	Small sample size; single-center; 48-hour follow-up may miss delayed symptom peaks; predominantly female sample;

	absence of pre-COVID baseline muscle data; applicability limited to nonhospitalized PCC without comorbidities.
Risk of bias	Moderate

Yasaci 2025

Author Reference	Yasacı et al. [26]
Year	2025
Country	Turkey
Study Design	Single-blind randomized controlled trial (prospective).
Setting	Gaziosmanpaşa Training and Research Hospital, Istanbul, Turkey.
Population	64 adults with post-COVID-19 syndrome (PCS) (32 in telerehabilitation group, 32 in control group); mean age 56 years; 47% female; symptoms ≥3 months; persistent dyspnea, pain, and functional limitations.
Inclusion criteria	Diagnosis of PCS by specialist; dyspnea score 2–3 on mMRC scale; age ≥18; ability to follow directions; access to technological facilities.
Exclusion criteria	SpO2 <92% at rest, systolic BP <90 mmHg, diastolic BP <60 mmHg, asthma/COPD, other lung diseases.
Interventions Participants (n) Drop-outs (n)	Telerehabilitation group: 6-week supervised TR program (2 sessions of 45 minutes/week) including breathing, relaxation, range-of-motion, walking, and squatting exercises; monitored via video conferencing. Intensity monitored on RPE scale. n=32 n=0
Control Participants (n) Drop-outs (n)	Unsupervised home exercise with same protocol. n=32 n=4

Follow up time points	Baseline and post-intervention (6 weeks) assessments.
Outcomes Measured	Primary: Dyspnea (mMRC), pain intensity (NPRS), functional capacity (5-TST). Secondary: Sleep quality (PSQI), anxiety and depression (HADS).
Results	Per protocol analysis. Difference in mean change between groups, mean (95% CI). mMRC: 0.8 (0.5 to 1.1), p = 0.001 Pain intensity (NPRS): 0.8 (0.3 to 1.4), p = 0.006 5-TST (seconds): 2.3 (0.9 to 3.8), p = 0.001 PSQI: 1.0 (0.2 to 1.9), p = 0.018 HADS-anxiety: 1.28 (0.4 to 2.1), p = 0.001 HADS-depression: 0.5 (-0.1 to 1.1) p = 0.124.
Limitations Noted	Per protocol-analysis; single-center; small sample size; moderate severity only (excluded severe cases); short follow-up (6 weeks); open-label to patients (only assessors blinded); self-reported adherence; no biomarker data; limited generalizability.
Risk of bias	Moderate

Zha 2024

Author Reference	Zha et al [27]
Year	2024
Country	China
Study Design	Randomized controlled trial (single-blind, prospective).
Setting	Renmin Hospital of Wuhan University, Wuhan, China.
Population	98 adults aged 18–70 years with post-acute sequelae of COVID-19 (PASC) after Omicron BA.5; symptoms of dyspnea

	and fatigue ≥12 weeks; median symptom duration ~22 weeks; 33 males, 62 females.
Inclusion criteria	Confirmed COVID-19 Omicron BA.5 (Dec 2022–Jan 2023); persistent symptoms ≥12 weeks; dyspnea and fatigue; age 18–70 years; any gender; informed consent.
Exclusion criteria	Acute COVID-19 in past 12 weeks; pregnancy/lactation; acute illness; recent MI (within the last three months), unstable angina, acute stroke (within the last six months); stage III hypertension; decompensated chronic renal failure; severe extracranial blood flow disorders; congenital heart/great vessel abnormalities; intellectual/mental disability; hypoxia intolerance.
Interventions Participants (n) Drop-outs (n)	IHE: Intermittent hypoxia exposure (5-min hypoxia alternating with 5-min normoxia, repeated five times/day, 10–12% O2) + routine therapy (e.g. inhaled bronchodilators and nebulized corticosteroids/anticholinergics as needed) for ≥7 days (median = 10 days). n=49 n=2
Control Participants (n) Drop-outs (n)	NE: Normoxia exposure + routine therapy (e.g. inhaled bronchodilators and nebulized corticosteroids/anticholinergics as needed) for ≥7 days (median = 10 days). n=49 n=1
Follow up time points	Baseline and post-intervention (after ≥7 days) assessments; no long-term follow-up.

Outcomes Measured	Primary: 6-minute walk distance (6MWD), spirometry (VT, FVC, FEV1, FEV1/FVC), Borg Dyspnea Scale, mMRC, Fatigue Assessment Scale (FAS), Chalder Fatigue Scale-11 (CFQ-11). Secondary: Adverse events, subjective improvement (dyspnea, fatigue), impact of IHE duration (<10 vs ≥10 days).
Results	Per protocol analysis. Change at post-intervention (after ≥7 days). 6MWD (meters): median (IQR) IHE: 47.0 (30.0, 61.0) NE: 23.5 (11.5, 33.0) V_T: median (IQR) IHE: 0.3 (0.2, 0.5) NE: 0.0 (-0.1, 0.2) FVC: median (IQR) IHE: 0.2 (0.1, 0.4) NE: 0.1 (0.0, 0.3) FVC % pred: median (IQR) IHE: 6.1 (4.2, 10.6) NE: 3.2 (-0.9, 8.8) FEV_1: median (IQR) IHE: 0.1 (0.1, 0.3)

	NE: 0.1 (0.0, 0.2) FEV_1 % pred: median (IQR) IHE: 5.3 (4.1 to 9.9) NE: 2.1 (-0.8 to 6.9) Borg Dyspnea Scale: median (IQR) IHE: 1.0 (0.0, 1.0) NE: 0.0 (0.0 to 1.0) mMRC: median (IQR) IHE: 0.0 (0.0, 1.0) NE: 0.0 (0.0, 0.0) FAS: median (IQR) IHE: 15.5 (13.0, 18.0) NE: 6.0 (5.0, 7.8) CFQ-11: median (IQR) IHE: 6.0 (4.0, 8.0) NE: 4.0 (2.0, 5.0) Subjective assessment of symptoms Improvement in dyspnea: n (%) IHE: 36 (76.6)

	NE: 19 (39.6) Improvement in fatigue: n (%) IHE: 39 (83.0) NE: 15 (31.3) No severe adverse events. 87.2% in IHE group and 79.2% in NE group experienced sleepiness.
Limitations Noted	Per protocol-analysis; small sample size; short duration (7–15 days); single-center; no biomarker analysis; focus on dyspnea/fatigue only (other PASC symptoms not assessed); lack of long-term follow-up.
Risk of bias	Moderate

Abbreviations

ACE-III = Addenbrooke's Cognitive Examination-III (cognitive assessment tool); **AE** = Aerobic Exercise; **AT** = Anaerobic Threshold; **BDI** = Beck Depression Inventory; **BDI-II** = Beck Depression Inventory-II; **BFSS** = Brief Fatigue Severity Scale; **BMI** = Body Mass Index; **BP** = Blood Pressure; **BPI** = Brief Pain Inventory; **BSIT** = Brief Smell Identification Test; **CAD** = Coronary Artery Disease; **CATS** = Cognitive Activation Theory of Stress; **CBT** = Cognitive Behavioral Therapy; **CFQ** = Cognitive Failures Questionnaire; **CFQ-11** = Chalder Fatigue Scale-11 (fatigue assessment); **CGI- I** = Clinical Global Impression-Improvement (scale); **CHD** = Coronary Heart Disease; **CK** = Creatine Kinase; **COPD** = Chronic Obstructive Pulmonary Disease; **CPE** = Clears-belong Plus (plant extract combination); **CPET** = Cardiopulmonary Exercise Test; **CPRP** = Cardiopulmonary Rehabilitation Program; **CRP** = C-Reactive Protein; **CS-30** = Chair Stand Test (30 seconds); **DASS - 21** = Depression Anxiety Stress Scales-21; **DLCO** = Diffusing Capacity of the Lungs for Carbon Monoxide; **DSM-5** =Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; **EQ-5D-5L** = EuroQol 5-Dimension 5-Level (quality of life questionnaire); **FAS** = Fatigue Assessment Scale; **FEV1** = Forced Expiratory Volume in one second; **5STS** = 5-repetition Sit-to-Stand test; **FSS-7** = Fatigue Severity Scale-7; **FVC** = Forced Vital Capacity; **GAD-7** = Generalized Anxiety Disorder Scale-7; **GHQ-12** = General Health Questionnaire-12; **HADS** = Hospital Anxiety and Depression Scale; **HIIT** = High-Intensity Interval Training; **HIT- 6** = Headache Impact Test-6; **HRmax** = Maximum Heart Rate; **HRQOL** = Health-Related Quality of Life; **IHE** = Intermittent Hypoxia Exposure; **IHMP** = Individualized Homeopathic Medicine Protocol; **IME** = Inspiratory Muscle Endurance; **IQR** = Interquartile Range; **ISI** = Insomnia Severity Index; **ITT** =Intention-To-Treat (analysis); **JNMCH** = Jawaharlal Nehru Medical College and Hospital; **LC19Ps** = Long-COVID-19 Patients; **MCS** = Mental Component Score/Scale; **MD** = Mean Difference; **MEP** = Maximal Expiratory Pressure; **MI** = Myocardial Infarction; **MICT** = Moderate-Intensity Continuous Training; **MIP** = Maximal Inspiratory Pressure; **mMRC** = Modified Medical Research Council (dyspnea scale); **MoCA** = Montreal Cognitive Assessment; **MRC** = Medical Research Council; **MS** = Multiple Sclerosis; **MYMOP-2** = Measure Yourself Medical Outcomes Profile version 2;

NCCHK = National Cardiovascular Center Harapan Kita; **NE** = Normoxia Exposure; **NMV/r** = Nirmatrelvir-ritonavir; **NPRS** = Numeric Pain Rating Scale; **NYHA** = New York Heart Association (heart failure classification); **O3-MAH** = Ozone Major Autohemotherapy; **OD** = Olfactory Dysfunction; **OFP** = Orofacial Pain; **PASC** = Post-Acute Sequelae of SARS-CoV-2 infection; **PBO/r** = Placebo-ritonavir; **PCF** = Peak Cough Flow; **PCR** = Polymerase Chain Reaction; **PCS** = Physical Component Score/Scale; also Post-COVID-19 Syndrome; **PCFS** = Post-COVID Functional Scale; **PEF** = Peak Expiratory Flow; **PEFR** = Peak Expiratory Flow Rate; **PEM** = Post-Exertional Malaise; **PGIC** = Patient Global Impression of Change; **PGIS** = Patient Global Impression of Severity; **PHQ-9** = Patient Health Questionnaire-9 (depression screening); **PMR** = Progressive Muscle Relaxation; **POMS** = Profile of Mood States; **PPP** = Per Protocol Population; **PR** = Pulmonary Rehabilitation; **PROMIS** = Patient-Reported Outcomes Measurement Information System; **PRP** = Platelet-Rich Plasma; **PSQI** = Pittsburgh Sleep Quality Index; **QOD** = Questionnaire of Olfactory Disorders; **QOD-NS** = Questionnaire of Olfactory Disorders—Negative Statements; **QOL** = Quality of Life; **RCT** - Randomized Controlled Trial; **RM** = Repetition Maximum (e.g., 1RM = one repetition maximum); **RMT** = Respiratory Muscle Training; **RPE** = Rating of Perceived Exertion; **RR** = Relative Risk; **RT-PCR** = Reverse Transcription Polymerase Chain Reaction; **SARS-CoV-2** = Severe Acute Respiratory Syndrome Coronavirus 2; **SD** = Standard Deviation; **SE** = Standard Error; **SF-12** = Short Form-12 Health Survey; **SF-36** = Short Form-36 Health Survey (quality of life questionnaire); **6MWD** = 6-Minute Walk Distance; **6MWT** = 6-Minute Walk Test; **6MWW** = 6-Minute Walk Work; **SNI** = Saline Nasal Irrigation; **SpO2** = Oxygen Saturation (peripheral); **SPHERE** = Somatic and Psychological Health Report; **SSTQ** = Singapore Smell and Taste Questionnaire; **ST** = Strength Training; **STS** = Sit-to-Stand (test); **THC** = Tetrahydrocannabinol; **TMT-A** = Trail Making Test Part A; **TMT-B** = Trail Making Test Part B; **TR** = Telerehabilitation; **TTH** = Tension-Type Headache; **TUG** = Timed Up and Go (test); **UPSIT** = University of Pennsylvania Smell Identification Test; **VAS** - Visual Analog Scale; **VO2** =Oxygen Consumption (volume of oxygen); **VPBM** = Vascular Photobiomodulation; **VT** = Tidal Volume; **WHO** = World Health Organization

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Inkluderade studier i rapporten ”Insatser vid postcovid och andra närliggande tillstånd och syndrom – en kartläggning Treatment and rehabilitation interventions for post-COVID and other related conditions and syndromes –a systematic mapping of studies”. Rapport 379 (2024)

Postcovid

Author	*Berenguel Senén*
Year	*2024*
Country	*Spain*
Ref #	*[1]*
Study design	*Open label RCT*
Setting	*Outpatient care*
Population	*Adults 18–65 years (mean 47 years, SD; 7.1, 73% female) with a history of COVID-19 >12 weeks after infection and with asthenia and dyspnea on exertion*
Follow up	*After treatment, at 8 weeks*
Intervention	*Therapeutic exercise training with both inhouse modality and a modality conducted at home with remote monitoring. Training was performed twice daily, six days a week for 8 weeks.*
Participants (n)	*25*
Drop-outs (n)	*7*
Comparison	*The control group received recommendations on physical exercise and healthy habits based on recommendations for the general population*
Participants (n)	*25*
Drop-outs (n)	*6*
Outcomes	*<u>Primary endpoint:</u> change in peak VO2* *Interventions group: peak VO2 significantly improved by 15% after the TPEP (pre- vs postintervention, 24.9% vs 29.3% mL/kg/min; p<0.001)* *Control group: showed no significant changes in peak VO2 (pre- vs postintervention, 25.2 vs 24.8 mL/kg/min; p=0 .46)* *Between group differences:* *Peak VO2, mL/kg/min intervention 29.3 (SD 4.7) vs. control 25.5 (SD 7.7), p0<.001* *<u>Secondary endpoints:</u>* *Quality of life scores:* *<u>PCFS</u>* *Intervention group 0 [0–1] vs control group 2 [0–2], p=0.015, in favour of active intervention* *<u>EQ5D-5L</u>* *Intervention group 6 [6–7] vs control group 7 [6–10], p=0.01, in favour of active intervention* *<u>PHQ-9</u>* *Intervention group 5 [4–9] vs control group 10 [5–14], p=0.03 in favour of active intervention* *Neuromuscular capacity:* *evaluated using load-velocity profiles for squat, bench press and pull down exercises* *<u>Squat</u>, p=0.43* *<u>Bench press</u>, p=0.16*

	Pull down, p=.02 in favour of active intervention *Additional outcomes were reported*
Comments	*Authors do not perform intention to treat analyses*
Risk of bias	*Moderate*

Author	*Berube*
Year	*2023*
Country	*Canada*
Ref #	*[2]*
Study design	*RCT, double-blind (triple?)*
Setting	*Self-administration outside health care setting*
Population	*Adults (mean age 44.9±7.4 (intervention) and 44.5±10.1, 66% female) with previously confirmed COVID-19 and persistent COVID-19-related olfactory dysfunction (≥2 months, UPSIT)*
Follow up	*End of treatment / 12 weeks post allocation*
Intervention	*Sniffing of four amber opaque glass vials, each containing an odor, twice daily for 12 weeks. Each session took 5 minutes and included a rotating exposure of each odor for 10 s, with 10 s rest intervals between each scent.*
Participants (n)	*25*
Drop-outs (n)	*Lost to follow-up: 5 Excluded from analysis: 2*
Comparison	*Sniffing of four amber opaque glass vials, containing odorless propylene glycole, twice daily for 12 weeks. Each session took 5 minutes and included a rotating exposure of each vial for 10 s, with 10 s rest intervals between each vial.*
Participants (n)	*25*
Drop-outs (n)	*3*
Outcomes	*Primary outcome:* *UPSIT-40 score (range 0-40?), higher = better, mean (SD)* *I: pre = 24.3 (7.01) post = 35.8 (7.95)* *C: pre = 24.6 (5.58) post = 25.6 (6.13)* *We did not observe any significant effect of group or time, nor any interaction on the UPSIT scores, (rm ANOVA). The number of days between onset of OD and difference in UPSIT scores were significantly and positively correlated (r(40) = 0.38; p = 0.016).* *Secondary outcomes:* *Self-evaluation smell and taste sensitivity, VAS (range 0-10)* *We did not observe an effect of group, but the interaction of group*time showed a trend (F(1,39) = 2.99; p = 0.091).* *Presence of parosmia yes/no, n* *After training, 14/19 participants from the trained group indicated parosmia, while this number was 21/22 in the placebo group (χ2 (1, 42) = 3.87, p = 0.049.* *Quality of Life* *We observed an effect of time (F(1,39) = 13.3; p = 0.001) on quality of life impairment but no effect of group or interaction* *I Nasal Obstruction Symptom Evaluation (NOSE), VAS (range "not a problem" to "severe problem")*
Comments	*Effects on Nasal Obstruction Symptom Evaluation (NOSE) does not seem to be reported.*

Risk of bias	*Moderate*

Author	*Calvo-Paniagua*
Year	*2024*
Country	*Spain*
Ref #	*[3]*
Study design	*RCT*
Setting	*Home-based tele-rehabilitation implemented by videoconference*
Population	*Adults 25–70 years (mean age about 49.4-50.8, women about 31.3-43.8%)) with moderate respiratory and/or functional impairments starting after the acute SARS-CoV-2 infection (mean duration after infection: 14.8 ± 1.7 months), at least 93% of oxygen saturation by pulse oximetry at rest on room air, n=64*
Follow up	*Post-intervention and 1 and 3 months after post-intervention*
Intervention	*A tele-rehabilitation program based on patient education, physical activity, airway clearing, and breathing exercise interventions, 18 sessions (40 minutes per session) in 7 weeks*
Participants (n)	*32*
Drop-outs (n)	*0*
Comparison	*Waitlist*
Participants (n)	*32*
Drop-outs (n)	*0*
Outcomes	*Primary outcome at post-intervention, mean change from baseline (95% CI):* *<u>Perceived physical exertion (MBDS):</u>* *I: −7.6 (–8.1; −7.2)* *C: 0.0 (–0.6; 0.5)* *Group* time interaction (multivariate lineal general model): p<0.001* *Secondary outcomes, mean change from baseline at post-intervention (95% CI):* *<u>Health-related quality of life (SGRQ):</u>* *I: 51.0 (–56.5; –45.6)* *C: 1.0 (–6.1; 8.0)* *Group* time interaction: p<0.001* *<u>6MWT test, walking distance (m):</u>* *I: 126.5 (38.7; 214.3)* *C: −40.1 (–105.4; 25.1)* *Group* time interaction: p<0.001oxygen saturation,* *Additional outcomes (oxygen saturation, heart rate, physical exertion severity) and follow-up times (1, and 3 months post-intervention) were reported*
Comments	*Not fulfilling the WHO criteria completely but the average post-infection time was 14.8 ± 1.7 months*
Risk of bias	*Moderate*

Author	*Capin*
Year	*2022*
Country	*USA*
Ref #	*[4]*
Study design	*RCT*
Setting	*Home environment/outside health care setting*
Population	*Adults (mean age 52 years, 47.7% female) discharged from hospital due to confirmed COVID-19 (with and without ICU stay)*

Follow up	*6 and 12 weeks*
Intervention Participants (n) Drop-outs (n)	*Multicomponent app-facilitated telerehabilitation program with e.g. physical exercises and lifestyle coaching, 12 individual sessions with licensed physical therapist during 9–10 weeks* *29* *1*
Comparison Participants (n) Drop-outs (n)	*No additional exercise equipment compared to material initially provided to both groups; educational handout about recovery from COVID-19 and weekly check-in phone calls* *15* *3*
Outcomes	*Primary outcome:* *<u>Feasibility (evaluated primarily by adherence and safety)</u>* *Adherence defined as percentage of 12 sessions attended, 9 sessions (75%) considered adherent.* *<u>Intervention group:</u>* *Adherence:* *27/29 participants met the threshold of at least 75% adherence: 93% (95% CI, 77 to 99)* *(24 participants met 100 % adherence)* *Adverse events:* *Total of 29 AEs (17 moderate and 12 minor) among 11 individuals.* *Proportion experiencing any AE was smaller in intervention group compared to control group (38% vs 60%, p=0.21).* *<u>Control group:</u>* *Adverse events:* *From baseline to week 12: 1 hospitalisation (severe AE) 5 weeks after enrolment.* *Total of 17 AEs (1 severe, 4 moderate and 12 minor) in 9 individuals.* *No deaths or life-threatening AEs in either group.* *Secondary outcomes:* *<u>Preliminary efficacy outcome measures: functional tests</u>* *(Performed remotely and facilitated by avatar in Health in Motion application, all models adjusted for treatment arm, visit, gender, age, BMI, duration of hospital stay and comorbidity index. Estimated change based on study population averages of male, age 53, BMI of 33, 5 days in the hospital and three comorbidities)* *<u>Physical function, 30 s chair stand (repetitions), change from baseline (95%CI):</u>* *Week 12:* *Intervention: 3.2 (1.8 to 4.6), p≤0.001* *Control: 5.1 (3.2 to 7.0), p≤0.001* *P-value for difference between groups: p=0.06* *See study for additional outcomes on physical function.*
Comments Risk of bias	*Assessor-blinded RCT* *Moderate*

Author	*Chen*
Year	*2021*
Country	*China*
Ref #	*[5]*
Study design	*RCT*

Setting	*Secondary care setting*
Population	*Participants (mean age 54.16±12.11 years (intervention) and 52.51±12.31 years (control)) were enrolled while hospitalized but according to inclusion criteria their condition also met discharge standards. Unclear time since covid-10 infection, thus not fulfilling WHO criteria for post COVID-19. Inclusion criteria involved presence of "Qi deficiency" according to traditional Chinese medicine.*
Follow up	*12 weeks*
Intervention	*Chinese medicine Bufei Huoxue capsules, 4 capsules 3 times daily for 90 days.*
Participants (n)	*64*
Drop-outs (n)	*7 (ITT-analysis was performed on 64)*
Comparison	*Placebo in same regimen as describe above.*
Participants (n)	*65*
Drop-outs (n)	*6 (but ITT-analysis on 65)*
Outcomes	*Note: outcomes do not seem to be calculated on all participants* *Primary outcome:* *<u>6-min Walk Distance</u>* *Mean difference: 34.2 (11.7–56.8) p=0.0022 in favour of tested intervention* *Secondary outcomes:* *<u>Fatigue score (FAI):</u>* *17.8 (–29.5 to –6.2), p=0.0019 in favour of tested intervention* *<u>St George's Respiratory Questionnaire:</u>* *–2.4 (–5.8 to 1.0) p=0.1148* *<u>Borg Dyspnea Score:</u>* *–0.1 (-0.5 to 0.2) p= 0.4801* *<u>Chinese medicine symptom complex score:</u>* *0.4 (–0.4 to 1.3) p=0.4723* *Additional outcomes were reported.*
Comments	*Possible that active treatment was distinguishable from placebo. Inclusion criteria included categorizations according to traditional Chinese medicine.*
Risk of bias	*Moderate*

Author	*Chung*
Year	*2023*
Country	*China*
Ref #	*[6]*
Study design	*RCT, open-label*
Setting	*Home environment/outside health care setting*
Population	*Adults aged ≥18 years with confirmed diagnosis of COVID-19 and with persistent (≥3 months) of olfactory disorder (median age 36 years (IQR 26.0–43.0), 56% female, 100% mild disease).*
Follow up	*4 weeks*
Intervention 1	*<u>Combination group:</u>* *Short-course (14 days) oral Vitamin A (25,000 IU soft gels) daily, in combination with OT (sequential exposures to four aromatic essential oils (lemon; eucalyptus; geranium; and cedarwood) delivered via aerosolisation diffuser units, 3 times/day for 4 weeks). During OT, study participants received 20 s of odorant exposures from each category, achieving aromatic stimulation for 80 s per treatment session.*

Participants (n)	*10*
Drop-outs (n)	*1*
Intervention 2	*Standard care:* *OT only, as described above*
Participants (n)	*11*
Drop-outs (n)	*3*
Comparison	*Control group:* *No intervention received during the study period*
Participants (n)	*5*
Drop-outs (n)	*5*
Outcomes	*Primary outcome* *Clinical improvements of olfactory function (improvement defined as a 2-point increase in BTT scores, measured differences in SIT scores):* *At end-of-treatment (4 weeks), a statistically significant difference was seen in mean BTT scores between groups (p<0.001).* *Mean BTT scores were significantly higher for the combination group compared to control, and compared to standard care groups:* *p<0.001, MD=4.4 (95% CI, 1.7 to 7.2); and p=0.009, MD=3.2 (95% CI, 0.5 to 5.9). There were no differences in BTT scores between standard care and control groups (p=0.229, MD=1.3, 95% CI, −0.9 to 3.4* *Intragroup comparisons of BTT scores between baseline and end-of-treatment MD (95% CI):* *Mean differences of BTT scores were significantly higher for the combination group compared to control; p=0.002, MD=3.3 (CI, 1.0 to 5.6), and standard care; p=0.012, MD=2.3 (CI, 0.3 to 4.2). No difference was seen in the MD of BTT scores between baseline and end-of-treatment.* *Secondary outcome: smell identification (SIT)* *There was a statistically significant difference in mean SIT scores between groups (p=0.043) at end-of-treatment. In the intragroup comparison, SIT scores were significantly higher in the combination group after treatment (p =0.009), but no differences were found in the standard care or control groups.*
Comments	*Small study,*
Risk of bias	*Moderate*

Author	*DalNegro*
Year	*2022*
Country	*Italy*
Ref #	*[7]*
Study design	*RCT Cross-over*
Setting	*Outpatient care*
Population	*Adults aged ≥18 years (mean age: 50.5±17.2 years, 62.5% female) with persistent dyspnea for 12–16 weeks after being defined "recovered" for COVID-19 pneumonia*
Follow up	*One week after treatment*
Intervention	*Nebivolol 2.5 mg once daily*
Participants (n)	*8+8 (cross-over)*
Drop-outs (n)	*0*
Comparison	*Placebo once daily*
Participants (n)	*8+8 (cross-over)*

Drop-outs (n)	*0*
Outcomes	*Several clinical and lung function variables were investigated* *<u>Nebivolol, but not placebo, improved:</u>* *Pre post Vital capacity (44.1±8.6 vs. 51.9±9.0), p=0.003* *Dyspnea score (2.5±0.8 vs. 0.6±0.3), p= 0.001* *More outcomes are reported in the article*
Comments	*Small study*
Risk of bias	*Moderate*

Author	*D'Ascanio*
Year	*2021*
Country	*Italy*
Ref #	*[8]*
Study design	*RCT*
Setting	*Outpatient care*
Population	*Adults aged 18–90 (mean age 42±14.1, 66.7% female) with a confirmed history of COVID-19 and anosmia/hyposmia persisting ≥90 days after negative COVID-19 nasopharyngeal swab. Severity of acute COVID-19 infection not stated.*
Follow up	*30 days*
Intervention	*Olfactory training/stimulation through Sniffin' Sticks (2/day for 10 min, for 30 days) and daily treatment with PEA/Luteolin oral supplement*
Participants (n)	*5*
Drop-outs (n)	*0*
Comparison	*Olfactory training/stimulation through Sniffin' Sticks (2/day for 10 min, for 30 days).*
Participants (n)	*7*
Drop-outs (n)	*0*
Outcomes	*<u>Change over time (T0–T1) in Sniffin scores (mean change)</u>* *I: 4* *C: 2* *The scores statistically significant different at T0 (p=0.01), but no statistical difference shown after 30 days (T1).* *(KW: p = 0.01)*
Comments	
Risk of bias	*Moderate*

Author	*DelCorral*
Year	*2023*
Country	*Spain*
Ref #	*[9]*
Study design	*RCT, with four groups*
Setting	*Home based training*
Population	*Adult COVID-19 survivors (71.6% female, 31.8% admitted to hospital, 5.7% admitted to ICU) with symptoms of fatigue and dyspnea for ≥2 months after COVID-19 infection.*
Follow up	*4, and 8 weeks post intervention. Only results of post intervention (8 weeks) tabulated.*
Intervention	*Two groups of homebased inspiratory respiratory OR inspiratory and expiratory (device with resistance) training 40 min/day (split in 20-minute sessions) 6 times a week for 8 weeks.*
Participants (n)	*22 + 22*
Drop-outs (n)	*1 + 1 in each group*

Comparison	*Two groups of homebased SHAM (device without resistance) inspiratory respiratory OR inspiratory and expiratory training 40 min/day (split in 20-minute sessions) 6 times a week for 8 weeks.*
Participants (n)	*22 + 22*
Drop-outs (n)	*1 +1 in each group*
Outcomes	*Group x time interaction, mixed way ANOVA. Change from baseline values.* *Health related quality of life (EQ-5D) with VAS of overall health* *There were statistically significant interactions between the time and group factors for HRQoL outcomes [EQ-5D-5L, index (F=2.459; p=0.031; h2=0.081) and VAS (F=3.373; p=0.004; h2 =0.108)]* *Exercise tolerance* *There were no statistically significant interactions between the time and group factors for exercise tolerance. There were no statistically significant between-group differences for exercise tolerance.* *Lung function* *The only lung function variable that showed a statistically significant group x time interaction was peak expiratory flow (PEF; F=3.612; p=0.003; h2 =0.114).* *Cognitive and psychological status* *There were no statistically significant interactions between the time and group factors for the cognitive and psychological status outcomes.* *There were additional outcomes reported.*
Comments	
Risk of bias	*Low*

Author	*Di Stadio*
Year	*2022*
Country	*Italy*
Ref #	*[10]*
Study design	*RCT, multicenter, double-blind*
Setting	*Self-administrated rehabilitation*
Population	*Outpatients aged 18–80 (65.4 % female, mean age 43.5 years) with confirmed history of COVID-19 and anosmia/hyposmia persisting ≥ 6 months (confirmed with extended version of Sniffin' Sticks psychophysical test). No data provided on previous possible hospitalisation due to COVID-19.*
Follow up	*90 days*
Intervention	*Daily treatment with oral supplement (PEA 700 mg + Lut 70 mg) as single dose, 5-10 minutes before breakfast plus olfactory training. Olfactory training entailed stimulation (Lemon, Rose, Eucalyptus, Cloves) 3 times per day for 6 minutes.*
Participants (n)	*130*
Drop-outs (n)	*0*
Comparison	*Olfactory training as noted for the intervention group + a daily placebo supplement therapy*
Participants (n)	*55*
Drop-outs (n)	*0*
Outcomes	*Group comparisons:* *Pre- and post- TDI scores (ANOVA):* *p<0.00001, F=13.23 – statistically significant differences* *Likelihood of recovery to normal TDI score (>31) at T3 (chi-square):* *Statistically significant differences favouring the intervention group, 56% resp. 10% respectively (p<0.00001).* *Only comparative results reported here. See study for more results from within the intervention- and control group.*
Comments	

Risk of bias	*Moderate*

Author	*Di Stadio*
Year	*2023*
Country	*Italy*
Ref #	*[11]*
Study design	*RCT, multicenter, double-blind study with four groups, one as active control*
Setting	*Outpatient treatment*
Population	*Outpatients aged 18–80 (mean age 37–42 years, apx 59% female) with confirmed history of COVID-19 and anosmia/hyposmia persisting ≥ 6 months (confirmed with extended version of Sniffin' Sticks psychophysical test). No data provided on previous possible hospitalisation due to COVID-19.*
Follow up	*90 days*
Intervention	*Three groups:* *1) Olfactory training + oral supplement (PEA 700 mg + Lut 70 mg) single dose once daily.* *2) Oral supplement (PEA 700 mg + Lut 70 mg) single dose once daily. No olfactory training.* *3) Oral supplement (PEA 700 mg + Lut 70 mg) single dose twice daily. No olfactory training.*
Participants (n)	*Group 1: 100; group 2: 50; group 3: 50*
Drop-outs (n)	*Group 1: 24; group 2: 2; group 3: 10*
Comparison	*Olfactory training as noted for the intervention group + a daily placebo supplement therapy*
Participants (n)	*50*
Drop-outs (n)	*12*
Outcomes	*<u>Group comparisons:</u>* *Outcomes based on Snifn' Sticks identification test scores where patients were classified as having subclinical recovery (<3 points), clinically significant recovery (≥3 points), unchanged (0-point change), or worsened (≥1 point decrement)* *Combined therapy (umPEA–LUT + olfactory training group) resulted in significantly more recovery than the other regimens ($\chi 2$: $p < 0.00001$)* *Improvements of ≥3 points where observed in 89.2% (50 patients; double weighted in randomization) receiving combined therapy group, 41.6% (20 patients) receiving um-PEA–LUT alone—once daily, 40% (16) patients) receiving um-PEA–LUT alone—twice daily, and 36.8% (14 patients) receiving olfactory training plus placebo*
Comments	*Analyses on based only on participates with full follow data.*
Risk of bias	*Moderate*

Author	*Elhamrawy*
Year	*2023*
Country	*Egypt*
Ref #	*[12]*
Study design	*RCT, 3-arm*
Setting	*Supervised exercise sessions*
Population	*Adults aged ≥60 years (mean age 65.7±3.6 (I1), 66.2±3.8 (I2) and 66.3±4 (control), 35.2% female) with COVID-19 with mild-to-moderate symptoms according to PCFS; 18 ≥3 months post-recovery*
Follow up	*Post-treatment*
Intervention 1	*Four 60-minute sessions of Tai Chi exercises weekly for 12 weeks*
Participants (n)	*18*

Drop-outs (n)	*0*
Intervention 2 Participants (n) Drop-outs (n)	*Four supervised 60-minute aerobic training sessions weekly for 12 weeks* *18* *0*
Comparison Participants (n) Drop-outs (n)	*Maintaining their usual ADLs* *18* *0*
Outcomes	*<u>Hand grip strength:</u>* *Mean difference (SE) in kg between groups* *Tai Chi vs control: –5.7 (1.2), p= 0.0001* *Aerobic training vs control: –3.2 (0.7), p= 0.0001* *Tai Chi vs aerobic training: –2.5 (1.2), p=0.0435* *<u>Fatigue severity scale:</u>* *Mean difference (SE) between groups* *Tai Chi vs control: 4.8 (1.4), p= 0.001* *Aerobic training vs control: 6 (1.2), p= 0.0001* *Tai Chi vs aerobic training: –1.2 (1), p=0.2491* *<u>30-second arm curls test:</u>* *Mean difference (SE) in number of repetitions between groups* *Tai Chi vs control: –4.3 (0.5), p= 0.0001* *Aerobic training vs control: –5.3 (0.3), p= 0.0001* *Tai Chi vs aerobic training: 1 (0.4), p= 0.0235* *<u>30-second chair stands test:</u>* *Mean difference (SE) in number of repetitions between groups* *Tai Chi vs control : –4 (0.4), p= 0.0001* *Aerobic training vs control: –4.4 (0.5), p= 0.0001* *Tai Chi vs aerobic training: 0.4 (0.4), p= 0.3618* *<u>8-Foot up and go test:</u>* *Mean difference (SE)* *Tai Chi vs control: 1.1 (0.2), p= 0.0001* *Aerobic training vs control: 1 (0.2), p= 0.0001* *Tai Chi vs aerobic training: 0.1 (0.2), p= 0.6021* *<u>2-minute step test:</u>* *Mean difference (SE) in number of steps between groups* *Tai Chi vs control: –7.8 (1.8), p= 0.0001* *Aerobic training vs control: –6.4 (1.3), p= 0.0001* *Tai Chi vs aerobic training: –1.3 (1.8), p=0.4689*
Comments Risk of bias	 *Low*

Author Year Country Ref #	*Espinoza-Bravo* *2023* *Spain* *[13]*
Study design Setting	*RCT* *Home-based exercise programmes instructed by a mobile phone application*

Population	*Adults aged 20–60 years (mean age 42.4 (SD 6.5) years; 79.1 % women) having a diagnosis of COVID-19 confirmed by PCR or an antigen test, the presence of at least 1 of certain persistent symptoms (fatigue, dyspnea, or functional limitation) for at least 6 weeks after infection, n=48*
Follow up	*8 weeks*
Intervention	*Functional exercise programme consisting of low-intensity strengthening exercise protocol for large muscle groups with increasing difficulty, 4–6 exercises per session, 25–40 minutes per week for 8 weeks*
Participants (n)	*24*
Drop-outs (n)	*3*
Comparison	*Aerobic exercise programme consisting of a progressive low-intensity walking protocol with weekly load adjustments, 25–45 minutes per week for 8 weeks*
Participants (n)	*24*
Drop-outs (n)	*2*
Outcomes	*Primary outcome at post-intervention, pre-post MD (95% CI):* *<u>Fatigue (FAS):</u>* *AE: −5.1 (−10.3 to 0.1)* *FE: −6.7 (−11.9 to −1.3)* *ns* *Secondary outcomes:* *<u>Activities of daily living (LCADL):</u>* *AE: −5.6 (−11.4 to 0.2)* *FE: −0.9 (−4.9 to 6.7)* *ns* *<u>30s standing test (repetitions):</u>* *AE: 1.2 (−1.0 to 3.4)* *FE: 2.6 (0.3 to 4.9)* *ns* *<u>Stress, PSS</u>* *AE: −6.2 (−10.3 to −2.1)* *FE: −4.9 (−9.1 to 0.8)* *ns* *<u>Depression (HADS-D):</u>* *AE: −2.0 (−4.8 to 0.4)* *FE: −0.5 (−3.0 to 2.0)* *ns* *<u>Anxiety (HADS-A):</u>* *AE. −1.0 (−3.1 to 1.2)* *FE: −0.1 (−2.3 to 2.1)* *ns* *<u>Quality of life (EQ-5D-5L):</u>* *AE: 0.1 (−0.1 to 0.2)* *FE: 0.1 (−0.2 to 0.2)* *ns* *<u>Global impression of change (PGIC), mean (SE):</u>* *AE: 4.0 (1.1)* *FE: 3.1 (1.5)*

	P= 0.042, favouring FE
Comments	*Not completely fulfilling the WHO criteria but an average of 17.4 months had passed since infection in the sample*
Risk of bias	*Moderate*

Author	*Fan*
Year	*2021*
Country	*China*
Ref #	*[14]*
Study design	*RCT, single-blind*
Setting	*Online/mobile phone intervention and counselling clinic at hospital*
Population	*COVID-19 patients (mean age 46±12.34 years, 62% female, 79% with mild symptoms) near discharge stage from hospital with positive screening results for posttraumatic stress symptoms (PTSS) Not fulfilling WHO criteria for post COVID-19 (long covid) but sufficiently long follow-up.*
Follow up	*6 months*
Intervention	*Narrative exposure therapy (NET, Schauer et al., 2011) and personalised psychological treatment. NET for 1–2 sessions/week for 8 weeks, 90~120 min.*
Participants (n)	*56*
Drop-outs (n)	*0*
Comparison	*Personalised psychological interventions based on the participants' symptoms (1 session/week, 40-60 min)*
Participants (n)	*55*
Drop-outs (n)	*0*
Outcomes	*<u>Effect of NET on PTSS (PCL-C) (time x group interaction, rm ANOVA):</u>* *PCL-C: significant ($F_{1,109}$=36.300, p<0.001), effect size: 0.143 (ηp 2)* *<u>Effect of NET on depression (SDS), anxiety (SAS), and sleep quality (PSQI), (time x group interaction, rm ANOVA):</u>* *SDS: <u>not</u> significant ($F_{1,109}$=0.957, p=0.329), effect size: 0.004 (ηp 2)* *SAS: <u>not</u> significant ($F_{1,109}$= 0.740, p=0.390), effect size: 0.003 (ηp 2)* *PSQI: <u>not</u> significant ($F_{1,109}$=0.124, p=0.011), effect size: 0.011 (ηp 2)*
Comments	
Risk of bias	*Moderate*

Author	*Figueiredo*
Year	*2024*
Country	*Brazil*
Ref #	*[15]*
Study design	*RCT, double-blind*
Setting	*Outpatient care, self-administration*
Population	*Adults aged 18–65 years (I: mean age 38.2 ± 11.3 years, 79.6% female; C: mean age 39.9 ± 13.3 years, 84.3% female) with previous confirmed SARS-CoV-2 infection (I: 93.9% mild disease; C: 93.9% mild disease) and olfactive disorder lasting ≥3 months, as well as smell loss confirmed by CCCRC test score <6.0* *12 weeks*
Intervention	*Olfactory training (kit with 4 odorants (rose, eucalyptus, lemon, cloves) to be sniffed twice a day for apx 10 s each) + alpha-lipoic acid: 300 mg tablet twice a day*
Participants (n)	*64*
Drop-outs (n)	*15*
Comparison	*Olfactory training as above + placebo*

Participants (n)	*64*
Drop-outs (n)	*13*
Outcomes	*Olfactory function (CCCRC score, mean±SD)* *I (n=49): 2.7±1.5 (baseline), 4.6±1.3 (12 weeks) – p-value (within group) <0.001* *C (n=51): 2.9±1.4 (baseline), 4.3±1.6 (12 weeks) – p-value (within group) <0.001* *p-value between groups: p=0.63* *Olfactory function (VAS score, median [IQR]* *I (n=49): 2.5 [0–5] (baseline), 6 [4–8] (12 weeks) – p-value (within group) < 0.001* *C (n=51): 3 [1–5] (baseline), 6.5 [5–8] (12 weeks) – p-value (within group) < 0.001* *p-value between groups: p=0.97*
Comments Risk of bias	 *Moderate*

Author Year Country Ref #	*Finnigan* *2023* *UK* *[16]*
Study design Setting Population Follow up	*RCT, double-blind* *Outpatient care, self-administration* *Adults aged 18–64 years (43.6 years, range 24–56; 68% female) with fatigue-dominant long COVID (total fatigue (bimodal) score of ≥8 on CFQ-11) and post-exertional skeletal muscle phosphocreatine recovery rate constant [τPCr] >50 s* *28 days post start of treatment*
Intervention Participants (n) Drop-outs (n)	*Oral AXA1125 (an endogenous metabolic modulator) 33.9g, reconstituted as a suspension in approximately 180 mL of water and administered twice daily for 4 weeks, with a minimal interval of 4 h between consecutive doses* *21* *0*
Comparison Participants (n) Drop-outs (n)	*Placebo administered in the same way as the active substance* *20* *0*
Outcomes	*Primary outcome was change in phosphocreatine rate – not tabulated here.* *Other outcomes:* *CFQ-11 Total fatigue Likert score (range 0-33) at 28 days, change from baseline, mean (SD):* *I: −5.25 (5.49)* *C: -2.25 (2.92)* *Least square MD (95% CI): -4.30 (-7.14 to -1.47), p=0.0039* *6-minute walk test (MWT) distance in meters, mean (SD):* *I: 25.57 (54.0)* *C: 25.3 (12.1)* *p>0.05 (ns) (MD not reported)* *Adverse events, number of patients:* *I: 11 (52%)* *C: 4 (20%)*
Comments	*Industry-funded study with some of the authors being employed and having options in the funding company*

Risk of bias	*Low*

Author	*Hansen*
Year	*2023*
Country	*Denmark*
Ref #	*[17]*
Study design	*RCT, cross-over. Washout period 4 weeks.*
Setting	*Primary care setting. Patients were recruited from a specialized post-covid condition outpatient clinic*
Population	*Adults (median age 49, range 22–70, 74.8% female), >2 persisting symptoms 12 weeks after confirmed COVID-19 (15.1% admitted to hospital during acute COVID-19 infection).*
Follow up	*End of treatment. 4 weeks after treatment.*
Intervention	*CoQ10 capsules in five 100-mg doses per day for 6 weeks*
Participants (n)	*121*
Drop-outs (n)	*2*
Comparison	*placebo capsules containing soy oil for 6 weeks*
Participants (n)	*121*
Drop-outs (n)	*2*
Outcomes	*Change in the number and/or severity of post-covid-condition-related symptoms after six weeks of CoQ10 treatment or placebo compared to baseline, measured as a symptom score and a health index.* *On average, the symptom scores were reduced by 5.18 points (95% CI, 3.40 to 6.95) after the six-week treatment with CoQ10, compared to a reduction of 4.04 points (95% CI to 2.13; 5.96) after receiving placebo. After adjusting for sequence and period, the mean difference in the change in symptom scores between CoQ10 and placebo was −1.18 (95% CI, −3.54 to 1.17) (p = 0.32).* *The estimated mean improvement in health index score was 0.04 (95% CI, 0.02 to 0.06) and 0.03 (95% CI, 0.006 to 0.05) after six weeks of CoQ10 treatment or placebo, respectively. After adjusting for period and sequence effect in the linear mixed-effects model, the estimated difference was 0.01 (95% CI, −0.02 to 0.04), which was not statistically significant (p = 0.40).* *The mean difference in symptom scores between baseline and week six was −5.85 points (95% CI, −8.21 to −3.48; p < 0.001), indicating that the participants in both arms improved significantly regardless of the treatment regimen in the first treatment period.* *Change in total symptom score in each of the seven clusters of the PCC-specific questionnaire were calculated as a post-hoc analysis*
Comments	
Risk of bias	*Low*

Author	*Hosseinpoor*
Year	*Iran*
Country	*2022*
Ref #	*[18]*
Study design	*RCT*
Setting	*Outpatient care setting*
Population	*Non-hospitalized adult patients (mean age 32.2 (intervention), 34.9 (control), 64.3% female) who had persistent anosmia or severe microsmia >4 weeks due to COVID-19.* *Not completely fulfilling WHO criteria for post COVID-19 (long covid)*
Follow up	*14 and 28 days after treatment*

Intervention Participants (n) Drop-outs (n)	*one puff of 0.05% wt/vol mometasone furoate (Raha Company, Iran) intranasal spray on each side twice per day for 4 weeks* *40* *5*
Comparison Participants (n) Drop-outs (n)	*one puff of 0.65% wt/vol sodium chloride nasal spray on each side (Decosalin, Raha Company, Iran) was administered to the patients in the placebo group twice daily for 4 weeks* *40* *5*
Outcomes	*<u>The Iran Smell Identification Test (Iran-SIT):</u>* *Changes in Smell Test (Iran-SIT) score between baseline and 4 weeks; mean (SD)* *I: 10.08 (4.22)* *C: 6.57 (3.62)* *p<0.001* *<u>Olfactory dysfunction, evaluated with visual analog scale (VAS, 0–10, higher = better)</u>* *Changes in VAS score between baseline and 4 weeks; mean (SD)* *I: 4.66 (2.36)* *C: 2.66 (2.26)* *p=0.001* *Frequence of anosmia and severe or mild microsmia at baseline and 2 and 4 weeks. Non-significant between group results at all time periods.* *No side effects were noted in the placebo and intervention groups of the study* *Additional outcomes were reported*
Comments Risk of bias	 *Low*

Author Year Country Ref #	*Ibrahim* *2023* *Saudi Arabia* *[19]*
Study design Setting Population Follow up	*Block RCT* *Outpatient setting* *Adults aged 60–80 (mean 62.6, 56.9% female, 23.6% with mild illness, 37.3% pneumonia, 37.5% severe penumonia)* *Not completely fulfilling WHO criteria for post COVID-19 (long covid)* *End of treatment (10 weeks)*
Intervention Participants (n) Drop-outs (n)	*Moderate intensity aerobic exercises 4 times per week for 10 weeks* *24* *0*
Intervention Participants (n) Drop-outs (n)	*Low intensity aerobic exercises 4 times per week for 10 weeks* *24* *0*
Comparison Participants (n) Drop-outs (n)	*Medical care and advice* *24* *0*
Outcomes	*Primary outcomes:* *<u>6-MWT, magnitude of change pre and post 10 weeks. Mean (SD), 95% CI:</u>* *Moderate intensity: 26.67 (13.21), 21.09 to 32.24*

	Low intensity: 14.71 (7.07), 11.72 to 17.69 *Comparison group: 0.63 /3.33), –0.78 to 2.03* *p= <0.01* *<u>PCFS, magnitude of change pre and post 10 weeks. Mean (SD), 95% CI:</u>* *Moderate intensity: –1.58 (0.50), –1.80 to–1.37* *Low intensity: –1.38 (0.65), –1.65 to –1.10* *Comparison group: –0.63 (0.71), –0.93 to –0.32* *p= <0.01* *Secondary outcomes:* *1-min STS, 36 subscales, HADS*
Comments Risk of bias	 *Low*

Author Year Country Ref #	*Jimeno-Almazan* *2022* *Spain* *[20]*
Study design Setting Population Follow up	*VO_2-max stratified RCT* *University medical center* *Non-hospitalised adults (45.2±9.5 years, 74.4% female) with confirmed COVID-19 and a chronic symptomatic phase, lasting >12 weeks from onset of symptoms* *End of treatment (8 weeks)*
Intervention Participants (n) Drop-outs (n)	*Training 3 days/week for 8 weeks: 2 days of resistance training combined with moderate intensity variable training and 1 day of light intensity continuous training* *19* *Not mentioned*
Comparison Participants (n) Drop-outs (n)	*WHO guidelines: Support for Rehabilitation: Self-Management after COVID-19 Related Illness, see comment* *20* *Not mentioned*
Outcomes	*Primary outcome:* *<u>PCFS post treatment mean (SD)</u>* *I: 1.1 (1.2)* *C: 1.8 (1.1)* *Group effect: p=0.033, ηp^2=0.15 (ANOVA)* *Other reported outcomes:* *<u>Pulmonary function:</u> FVC (L), %FVC, FEV-1 (L), %FEV-1, FEV-1/FVC, FEV25-75% (L·s–1), MVV (L), %MVV* *<u>Quality of life and fatigue:</u> SF-12 (PA), SF-12 (MH), mMRC, CFQ-11 (bimodal), CFQ-11 (Likert), FSS, DSQ-14, PCSF* *<u>Anxiety and depression:</u> GAD-7, PHQ-9* *<u>Cardiovascular fitness:</u> VO_2max (ml/kg/min), Final RPE 6–20, Final HR (b·m–1)*

	Muscular strength: Sit-to-stand (s), Handgrip (kg), BP-50% 1RM (m·s−1), HSQ-50% 1RM (m·s−1), Leg extension (N)
Comments	*WHO guidelines: support for rehabilitation involves recommendation of aerobic exercise for 20-30 minutes 5 times a week.*
Risk of bias	*Moderate*

Author	*Jimeno-Almazan*
Year	*2023*
Country	*Spain*
Ref #	*[21]*
Study design	*VO_2-max stratified RCT*
Setting	*Outpatient care setting*
Population	*Non-hospitalised adults (45.3±8.0 years, 68.8% female) with confirmed COVID-19 and a chronic symptomatic phase, lasting >12 weeks from onset of symptoms*
Follow up	*End of treatment (8 weeks)*
Intervention	*Concurrent training (CT): a three-days-a-week concurrent training routine: two days of resistance training followed by moderate intensity variable training and one day of a monitored autonomous light intensity continuous training*
Participants (n)	*21*
Drop-outs (n)	*1*
Intervention	*Inspiratory muscle training (RM): inspiratory muscle training protocol with PowerBreath Classic Heath Series mechanic threshold devices*
Participants (n)	*17*
Drop-outs (n)	*0*
Intervention	*Concurrent training as above plus inspiratory muscle training as above (CTRM)*
Participants (n)	*25*
Drop-outs (n)	*2*
Comparison	*Advised to follow WHO guidelines: "Support for Rehabilitation: Self-Management after COVID-19-Related Illness"*
Participants (n)	*20*
Drop-outs (n)	*0*
Outcomes	*Main outcomes:* *Cardiorespiratory fitness, measured as:* *VO_2max* *Following the 8 wk-intervention period, no significant differences between groups were detected in the estimated VO_2max ($P > 0.05$).* *Muscle strength:* *Lower body maximal and submaximal strength (squat 1RM and MPVALL)* *Between groups effects not reported* *Upper body submaximal strength (Bench Press MPVALL)* *Authors report significant interaction for upper body submaximal strength (Bench Press MPVALL) ($P < 0.05$) for CT and CTRM groups.* *Dominant hand grip strength* *No inter- or intragroup interactions were found for the dominant hand grip strength.* *Secondary outcomes:* *PCFS, mMRC <2, PHQ9 <10, GAD7 <10, FSS <4, CFS <18, SF-12 PA, SF-12 MH, number of symptoms, frequency of 10 specific symptoms*

	After 8 wk-intervention period, no significant differences between groups were detected in the mMRC (dyspnea), GAD-7 (anxiety), PCFS (functional status), and SF-12 PA and MH (health-related quality of life). *Additional outcomes reported*
Comments	*Study uses same study protocol as [20].*
Risk of bias	*Moderate*

Author	*Kerget*
Year	*2023*
Country	*Turkey*
Ref #	*[22]*
Study design	*RCT*
Setting	*Outpatient care*
Population	*Adults aged >18 (60% female, 62.6±8.1 years (intervention) and 68.4±9.8 years (control)) with confirmed COVID-19, presented with symptoms, having fibrosis secondary to COVID-19 on radiological imaging, not requiring intubation and mechanical ventilation during acute COVID-19*
Follow up	*12 weeks post start of treatment*
Intervention	*Pirfenidone (an antifibrotic agent, off-label use) oral tablets, 600 mg/day the first week, 1200 mg/day the second week, and 1800 mg/day the third week*
Participants (n)	*15*
Drop-outs (n)	*0*
Comparison	*Nintedanib (an antifibrotic agent, off-label use), oral tablets 300 mg/day*
Participants (n)	*15*
Drop-outs (n)	*0*
Outcomes	*<u>6-minute walk test (MWT) distance in meters, mean change from baseline (SD):</u>* *I: 29.8 (27.2)* *C: 70 (48.4)* *P<0.05* *<u>Forced vital capacity (FVC), liters, mean change from baseline (SD):</u>* *I: 0.2 (0.3)* *C: 0.4 (0.3)* *P=0.17* *<u>Forced expiratory volume (FEV), liters, mean change from baseline (SD):</u>* *I: 0.2 (0.3)* *C: 0.2 (0.2)* *P=0.66* *<u>Heart rate, mean change from baseline (SD):</u>* *I: −12.9 (11.6)* *C: 10.2 (7.4)* *P=0.46* *<u>S02, finger tip saturation:</u>* *I: 5.6 ± 4.8* *C: 10.6 ± 4.1* *P=0.005*

	Adverse events, number of patients: *Diarrhea: I: 0, C: 12 (80%)* *Nausea-vomiting: I: 1 (6.6%), C: 10 (66.6%)* *Loss of appetite: I: 1 (6.6%), C: 4 (26.6%)* *Rash: I: 1 (6.6%) C: 0* *Photosensitivity: I: 1 (6.6%), C: 0*
Comments	
Risk of bias	*Moderate*

Author	*Kerling*
Year	*2024*
Country	*Germany*
Ref #	*[23]*
Study design	*RCT*
Setting	*Outpatient care*
Population	*Volunteers ≥18 years (mean age 46.2 (SD 11.2) years, 67,7% women) with a continuing impairment of physical or mental health after COVID-19 (detection by polymerase chain reaction) infection with a fatigue assessment scale (FAS) score of 22 points.*
Follow up	*After treatment (3 months)*
Intervention	*Individually designed exercise plan recommending 150 min of moderate physical activity per week (60–75% of the maximum heart rate measured during the incremental exercise test)*
Participants (n)	*35*
Drop-outs (n)	*5*
Comparison	*Asked to continue with their current lifestyle and everyday activities*
Participants (n)	*37*
Drop-outs (n)	*5*
Outcomes	*Primary outcome:* *V̇O2peak (ml/min/kg) mean difference (95% CI) between groups over time* *–0.6 (–1.8 to 0.8)* *Secondary outcomes:* *FAS mean difference (95% CI) between groups over time* *0.3 (–2.6 to 3.9)* *SF-36 MCS mean difference (95% CI) between groups over time* *–3.0 (–8.5 to 2.5)* *SF-36 PCS mean difference (95% CI) between groups over time* *1.2 (–2.7 to 5.1)* *HADS-D depression mean difference (95% CI) between groups over time* *1.0 (–0.7 to 2.8)* *HADS-D anxiety mean difference (95% CI) between groups over time* *0.2 (–1.4 to 1.6)* *WAI mean difference (95% CI) between groups over time* *1.0 (–1.9 to 3.8)* *FEV1 (l) mean difference (95% CI) between groups over time*

	–0.05 (–0.18 to 0.07) *<u>FEV1 predicted (%) mean difference (95% CI) between groups over time</u>* *1.69 (–2.00 to 5.39)* *<u>VC (l) mean difference (95% CI) between groups over time</u>* *0.00 (–0.15 to 0.16)* *<u>VC predicted (%) mean difference (95% CI) between groups over time</u>* *–0.08 (–3.69 to 3.52)*
Comments Risk of bias	 *Moderate*

Author Year Country Ref #	*Klirova* *2024* *Czech Republic* *[24]*
Study design Setting Population Follow up	*RCT, double-blind* *Medical facility* *Adults aged 18–75 years (70% female, mean age 42.2 ±10.5); COVID-19 negativity at the time of pre-study entry; symptom duration >1 month after detection of COVID-19; FIS score ≥40; presence of neuropsychiatric symptoms of PASC (A-PASC, minimum total score ≥25); possible psychopharmacological medication on a stable dose for ≥4 weeks.* *8 weeks*
Intervention Participants (n) Drop-outs (n)	*Transcranial direct current stimulation (tDCS)* *17* *1*
Comparison Participants (n) Drop-outs (n)	*Sham-tDCS* *18* *1*
Outcomes	*At 8 week follow-up (time x condition intergroup differences, LS mean difference, Sidak-corrected)* *<u>Fatigue (FIS total score changes)</u>* *tDCS vs sham: 11.3 (95% CI, −11.7 to 34.4), t=1.31, p_{corr}=0.7 – not significant* *sham: −27.1 (95% CI, −45.2 to −9.1), t=4.40, p_{corr}<0.001* *active: −15.8 (95% CI, −33.7 to 2.1), t=2.59, p_{corr}=0.13* *<u>Anxiety (GAD-7 self-assessment score changes)</u>* *tDCS vs sham: 0.33 (95% CI, −4.02 to 4.67), p=1.000 – not significant* *<u>Depression (PHQ-9 self-assessment score changes)</u>* *tDCS vs sham: 0.88 (95% CI, −3.29 to 5.04), p=0.997 – not significant* *<u>Quality of life (AQoL−6D total score changes)</u>* *tDCS vs sham: −3.23 (95% CI, −12.25 to 5.79), p=0.939 – not significant* *See study for domain specific results within FIS and AQoL−6D*
Comments Risk of bias	 *Moderate*

Author	*Kogel*
Year	*2023*
Country	*Germany*
Ref #	*[25]*
Study design	*RCT*
Setting	*Outpatient training program*
Population	*Participants, aged ≥18 years (mean age 42.7 (SD 13.4) years, 61% women) were recruited from a post covid clinic. Parti cants should have sustained fatigue (defined as >50 points with four or more dimensions affected on the MFI-20-questionnaire) at a minimum of 6 weeks after a COVID-19. The mean age was 42.7±13.4 years and 61% were females.*
Follow up	*Follow up after intervention (4 weeks) and after 3 and 6 months.*
Intervention	*4 weeks of two to three times weekly personalized strength endurance training.*
Participants (n)	*29*
Drop-outs (n)	*9 (at 6 months follow up)*
Comparison	*Care as usual, with no restrictions on exercise.*
Participants (n)	*28*
Drop-outs (n)	*8 (at 6 month follow up)*
Outcomes	*There were various significant between group effects at the assessment after 4 week intervention, not tabulated here.* *Outcomes at 3 and 6 monhts :* *Strenings measurements* *Cardiopulmonary* *Fatigue, assessed with Multidimensional Fatigue Inventory-20* *Quality of life, assessed with McGill Quality of Life Questionnaire (MQOL)* *Functional status, assessed with Post-COVID-19 Functional Status (PCFS)* *After 3 months:* *no significant differences between the groups in any of the questionnaires or subdomains.* *At 6 months:* *The subdomain of psychological quality of life (MQOL) was significantly better in the exercise group than in the control group (exercise 29±9 vs. control 25±9, p<0.05)* *Physical activity* *The total physical activity per week was significantly greater in the exercise group than in the control group assessed with GPAQ (exercise 1280±1192 vs. control 644±554, p<0.05)* *Additional outcomes were reported*
Comments	
Risk of bias	*Moderate*

Author	*Kuut*
Year	*2023*
Country	*The Netherlands*
Ref #	*[26]*
Study design	*RCT*
Setting	*Online intervention*

Population	*Adults aged ≥18 (mean age 45.7±12.4 (intervention) and 46.0±12.9 (control), 72.8% female, 89% non-hospitalised during initial infection) with severe fatigue (≥35 on the CIS-fatigue) and limitations in physical functioning (≤65 on physical functioning subscale of SF-36) and/or social functioning (≥10 on WSAS) following COVID-19 infection*
Follow up	*19 weeks, 6 months*
Intervention	*CBT for fatigue post COVID-19 infection (Fit after COVID), blended intervention developed by adapting existing CBT protocols for severe fatigue in long-term medical conditions*
Participants (n)	*57*
Drop-outs (n)	*11*
Comparison	*Care as usual*
Participants (n)	*57*
Drop-outs (n)	*4*
Outcomes	***Primary outcome:*** *Fatigue Mean (SE) at T0, T1, T2:* *(Higher score on CIS-fatigue-scale indicates more severe fatigue, ≥35 indicates severe fatigue)* *CBT: 47.8 (0.7), 30.6 (1.4), 31.5 (1.7)* *CAU: 47.0 (0.8), 39.9 (1.4), 39.9 (1.7)* *Overall between-group difference, Mean (95% CI):* *−8.8 (−11.9 to −5.8), p<0.001* *Cohen's d of the overall effect: 0.69* ***Secondary outcomes:*** *Overall between-group difference, Mean (95% CI):* *Physical functioning (self-rated, SF-35 PF): 7.1 (2.9 to 11.3), P=0.001* *Social functioning (WSAS score): −6.6 (−9.1 to −4.2), P<0.001* *Somatic symptoms (PHQ-15): −2.0 (−2.9 to −1.0), P<0.001* *Problems concentrating (CIS-conc): −5.1 (−6.9 to −3.4), P<0.001* *All significant results represent mean difference based on two follow-up timepoints and were all in favour of CBT. Eight adverse events were recorded during CBT, and 20 during CAU. No serious adverse events were recorded.*
Comments	
Risk of bias	*Moderate*

Author	*Lasheen*
Year	*2023*
Country	*Egypt*
Ref #	*[27]*
Study design	*RCT, double-blind*
Setting	*Outpatient care, self-administration*
Population	*Adults (21 to 56 years, mean 33 vs 32 years), 55% women, with olfactory dysfunction (anosmia, hyposmia, or parosmia) >3 months post-COVID-19, with complete recovery from COVID-19, n=40*
Follow up	*End of treatment / 2 months post-allocation*
Intervention	*Corticosteroids, 8 doses over 2 months (twice weekly) injected in the olfactory mucosa*

Participants (n)	*20*
Drop-outs (n)	*0*
Comparison	*Placebo injections (saline)*
Participants (n)	*20*
Drop-outs (n)	*0*
Outcomes	*QOD-NS (range 0-51) post-intervention, mean (SD)* *I: 7.60 (8.91)* *C: 12.40 (12.00)* *ns*
Comments	
Risk of bias	*Moderate*

Author	*Lau*
Year	*2024*
Country	*China*
Ref #	*[28]*
Study design	*Double blinded RCT*
Setting	*Outpatient setting*
Population	*Adults aged ≥18 (mean age about 49 years, females about 65%) with laboratory verified SARS-CoV-2 infection with at least one post acute covid 19 symptom (according to PACSQ-14) for ≥4 weeks. Thus, participants did not fully fulfil the WHO-criteria.*
Follow up	*3 and 6 months*
Intervention	*Oral synbiotic preparation (SIM01, with 20 billion colony forming units of three bacterial strains: B adolescentis, B bifidum, and B longum) administrated as sachets twice daily*
Participants (n)	*232*
Drop-outs (n)	*28 (at 6 month follow up)*
Comparison	*Placebo, which consisted of low dose vitamin C 1 mg twice daily*
Participants (n)	*231*
Drop-outs (n)	*32 (at 6 month follow up)*
Outcomes	*Primary outcome:* *<u>Symptoms assessed with PACSQ-14 (OR, 95% CI):</u>* *At 6 months, a significantly higher proportion of individuals who received SIM01 had alleviations in* *- fatigue (2.273, 1.520 to 3.397), p=0.0001* *- memory loss (1.967, 1.271 to 3.044), p=0.0024* *- difficulty in concentration (2.644, 1.687–4.143), p<0.0001* *- gastrointestinal upset (1.995, 1.304–3.051, p=0.0014* *- general unwellness (2.360, 1.428–3.900, p=0.0008)* *compared with placebo, after adjusting for multiple comparisons* *Secondary outcomes:* *<u>Quality of life (VAS at 6 months, aided by trained interviewers, mean (SD))</u>* *SIM01: 76.0 (SD 12.0)* *Placebo: 74.5 (12.3)* *p=0.17* *<u>Physical activity (IPAC at 6 months, median (IQR)):</u>* *Post-hoc analysis showed no significant difference in total metabolic equivalent of task minutes/week between the two groups* *SIM01: 1646.3 (IQR 815.6–2899.5)* *Placebo: 1902.0, 956.0–3290.0* *p=0.37*

	Additional results were reported
Comments	*Although blinded, it is likely that participants may have realized their group allocation.*
Risk of bias	*Moderate*

Author	*Lerner*
Year	*2023*
Country	*United States*
Ref #	*[29]*
Study design	*RCT*
Setting	*Primary care setting*
Population	*Adults aged ≥18 (78.6% female, IG: mean age 41.5±14.6, CG: mean age 40.7±12.7) with self-reported new-onset olfactory dysfunction and clinically suspected or laboratory-confirmed SARS-CoV-2 infection. No data provided on previous possible hospitalisation due to COVID-19.* *Not completely fulfilling WHO criteria for post COVID-19, but authors do themselves consider the study population to demonstrate persistent covid-related OD.*
Follow up	*6 weeks*
Intervention	*Daily capsules of 2000 mg omega-3 fatty acid supplementation.*
Participants (n)	*70*
Drop-outs (n)	*13*
Comparison	*Placebo*
Participants (n)	*69*
Drop-outs (n)	*9*
Outcomes	*Primary outcome:* *<u>Change in BSIT score between-group difference at 6 weeks, 95% CI:</u>* *−0.43 (−1.13 to 0.27), as SMD: 0.228 (−0.15 to 0.59), p=0.221* *<u>Quality of life (modified brief QOD-NS survey):</u>* *No significant difference over time in the two groups (β=0.004, p =0.96)* *Secondary outcome:* *<u>SNOT-22 (Sino-Nasal Outcome Test-22):</u>* *No significant difference between groups over time (β =0.1605, p=0.462)*
Comments	*No ITT-analyses.*
Risk of bias	*Moderate*

Author	*Li*
Year	*2021*
Country	*China*
Ref #	*[30]*
Study design	*RCT, multicenter*
Setting	*Home-based, outside health care setting*
Population	*Adults aged 18–75 years (55.5% female, mean age: 50.6 years) discharged after inpatient treatment for COVID-19 (68.1% not severe, 86.6% oxygen support or non-invasive ventilation), with a mMRC dyspnoea score of 2–3.* *Not completely fulfilling WHO criteria for post COVID-19 (long covid)*
Follow up	*~28 weeks*

Intervention	*Unsupervised home-based 6-weekexercise programme comprising breathing control and thoracic expansion, aerobic exercise and LMS exercise, delivered via smartphone, and remotely monitored with heart rate telemetr.*
Participants (n)	*59*
Drop-outs (n)	*23*
Comparison	*Short education at baseline.*
Participants (n)	*61*
Drop-outs (n)	*5*
Outcomes	*Functional exercise capacity:* *<u>Adjusted between-group difference in change in 6MWD from baseline (treatment effect):</u>* *Post-treatment (6 weeks): 65.45 m (95% CI, 43.80 to 87.10; p<0.001)* *Follow-up (apx 28 weeks): 68.62 m (95% CI, 46.39 to 90.85; p<0.001)* *Perceived dyspnoea:* *<u>mMRC perceived dyspnoea, to favourable outcome (mMRC=0):</u>* *Post-treatment (6 weeks): 1.46 (95% CI, 1.17 to 1.82; p=0.001)* *Follow-up (apx 28 weeks): 1.22 (95% CI, 0.92 to 1.61; p= 0.162)* *Health-related quality of life:* *<u>SF-12 PCS (higher scores indicating better health):</u>* *Post-treatment (6 weeks): 3.79 (95% CI, 1.24 to 6.35; p=0.004)* *Follow-up (apx 28 weeks): 2.69 (95% CI, 0.06 to 5.32; p= 0.045)* *<u>SF-12 MCS (higher scores indicating better health):</u>* *Post-treatment (6 weeks): 2.18 (95% CI, –0.54 to 4.90; p= 0.116)* *Follow-up (apx 28 weeks): 1.99 (95% CI, –0.81 to 4.79; p= 0.164)*
Comments	
Risk of bias	*Moderate*

Author	*Longobardi*
Year	*2023*
Country	*Brazil*
Ref #	*[31]*
Study design	*RCT, single-blind*
Setting	*Primary care/home-based*
Population	*Survivors (mean age 60.8±7.1 years (intervention) and 61.2±7.7 (control), 50% female) of severe/critical COVID-19 (5±1 months after intensive care unit discharge)*
Follow up	*16 weeks post study start (end of treatment)*
Intervention	*A home-based semi-supervised exercise training programme, 3 sessions a week for 16 weeks*
Participants (n)	*25*
Drop-outs (n)	*4*
Comparison	*Standard of care including general advice for a healthy lifestyle*
Participants (n)	*25*
Drop-outs (n)	*5*
Outcomes	*Post-intervention between-group differences, adjusted MD (95% CI)* *<u>SF-36 physical functioning:</u>* *16.8 (5.8 to 27.9), p=0.005, favours intervention* *<u>SF-36 general health</u>* *17.4 (1.8 to 33.1) p=0.024, favours intervention*

	<u>Cardiorespiratory fitness, time to exhaustion (s)</u> *81.6 (–58.9 to 222.2) p=0.406* *<u>Pulmonary function, FEV (L)</u>* *–0.16 (–0.77 to 0.44) p=0.881* *<u>Handgrip strength, kg</u>* *2.42 (–6.33 to 11.15) p= 0.879* *Also reported: Self-reported presence of persistent symptoms (no significant differences), several additional outcomes*
Comments Risk of bias	 *Moderate*

Author Year Country Ref #	*McGregor* *2023* *UK* *[32]*
Study design Setting Population Follow up	*Multicenter RCT* *Home-based online-delivered intervention* *Adults (26–86 years, mean 56 years, 52% women) discharged from NHS hospitals at least three months previously after covid-19 and with ongoing physical and/or mental health sequelae, n=585* *3, 6 and 12 months*
Intervention Participants (n) Drop-outs (n)	*Rehabilitation Exercise and psychological support (REGAIN) programme, consisting of weekly home based, live, supervised, group exercise and psychological support sessions (1 h each) delivered online for 8 weeks* *298* *82*
Comparison Participants (n) Drop-outs (n)	*Usual care (a single online session of advice and support)* *287* *61*
Outcomes	*Outcomes at 3 months, adjusted MD (95% CI):* *Primary outcome:* *<u>Health related quality of life, PROPr score:</u>* *0.03 (0.01 to 0.05), P=0.02* *Secondary outcomes:* *<u>Fatigue, PROPr subscale score:</u>* *2.50 (1.19 to 3.81), P<0.001* *<u>HADS anxiety:</u>* *0.29 (–0.37 to 0.94), P=0.38* *<u>HADS depression:</u>* *0.46 (–0.14 to 1.05), P=0.13* *<u>Physical activity, IPAQ-SF (MET min/week):</u>* *1.66 (1.14 to 2.41), P=0.01* *The effect on health related quality of life (PROPr score) was sustained at 12 months*

	Additional outcomes were reported
Comments	
Risk of bias	*Måttlig*

Author	*McIntyre*
Year	*2023*
Country	*Canada*
Ref #	*[33]*
Study design	*RCT, double-blind*
Setting	*Primary care*
Population	*Adults (mean age 43.65±12.26 in intervention group, 44.94±12.03 in control group, 65.8% female) with a history of confirmed SARS-CoV-2 infection who met WHO-defined 19 criteria for PCC*
Follow up	*8 weeks*
Intervention	*Vortioxetine (multimodal antidepressant). Participants aged 18–65 years: 10 mg/day week 1–2, 20 mg/day week 3–8. Participants aged 65+: 5 mg/day during week 1–2, 10mg/day week 3–8*
Participants (n)	*75*
Drop-outs (n)	*7*
Comparison	*Placebo*
Participants (n)	*74*
Drop-outs (n)	*1*
Outcomes	*<u>Cognitive function (DSST total score)</u>* *Between-group analysis (unadjusted) did not show a significant difference in the overall change in cognitive function: MD (SE): 0,157 (0,171); 95% CI, –0.179 to 0.492; p=0.361* *In the fully adjusted model, a significant treatment × time interaction was observed in favour of vortioxetine with baseline CRP as a moderator (p=0.012)* *A significant improvement in DSST scores were observed in vortioxetine versus placebo treated participants in those whose baseline CRP was above the mean (p=0.045)* *<u>Depressive symptoms (QIDS-SR16 total score)</u>* *A significant treatment x time interaction, $\chi 2=4.837$, p=0.028 was observed after adjusting for age, sex, education, and baseline QIDS-SR-16 total score* *Significant group ($\chi 2=4.653$, p=0.031) and time (χ =49.184, p<0.001) effects were also observed* *A significant between-group difference was also observed:* *MD (SEM)=–1.516 (0.679), 95% CI,–2.847 to –0.185, p = 0.026* *<u>HRQoL (WHO-5 total score)</u>* *A significant treatment x time interaction, $\chi 2=7.893$, p = 0.005 was observed after adjusting for age, sex, education, and baseline WHO-5 total score* *Significant group ($\chi 2$ 11 = 8.675, p = 0.003) and time ($\chi 2$ = 29.69, p < 0.001) effects were also observed, indicating that participants' WHO-5 scores significantly improved over time and at significantly different rates within each treatment group* *A significant between-group difference was observed:* *MD (SEM)=2.356 (0.807), 95% CI, 0.774 to 3.938, p=0.004*

Comments	
Risk of bias	*Moderate*

Author	*McNarry*
Year	*2021*
Country	*United Kingdom*
Ref #	*[34]*
Study design	*RCT*
Setting	*Primary care setting*
Population	*Adults (mean age 46.6±12.2 years; 88% female) recovering from self-reported COVID-19 (9.0±4.2 months post-acute infection) with breathlessness. No data provided on previous possible hospitalisation due to COVID-19.*
Follow up	*8 weeks*
Intervention	*Inspiratory Muscle Training, 3 unsupervised sessions/week for 8 weeks, with a handheld inspiratory flow resistive device that wirelessly syncs to a mobile device via an App to provide graphical biofeedback.*
Participants (n)	*224*
Drop-outs (n)	*113*
Comparison	*"Usual care" waitlist control*
Participants (n)	*57*
Drop-outs (n)	*20*
Outcomes	*<u>Health-related quality of life (K-BILD total score):</u>* *No between-group difference post-intervention* *I: 58.2±12.3* *C: 59.5±12.4* *p<0.05* *See study for additional results on several secondary outcomes on respiratory function (no significant between-group differences post-intervention based on ITT-analysis).*
Comments	
Risk of bias	*Moderate*

Author	*Momtazmanesh*
Year	*2023*
Country	*Iran*
Ref #	*[35]*
Study design	*RCT, double-blind*
Setting	*Self-administration outside health care setting*
Population	*Patients aged 18–65 (mean age 37.32±9.59 (intervention) and 35.16±8.24 (control), 46% female) with a history of COVID-19-related hospitalisation, and at least 20 days since onset, and 7 days since last day of symptoms; MMSE ≤23 or MoCa ≤22.* *Not completely fulfilling WHO criteria for post COVID-19)*
Follow up	*6 and 12 weeks*
Intervention	*Famotidine (40 mg, twice daily for 12 weeks)*
Participants (n)	*29*
Drop-outs (n)	*7 (Week 6: 5, week 12: 2)*
Comparison	*Placebo*
Participants (n)	*29*
Drop-outs (n)	*7 (Week 6: 5, week 12: 2)*
Outcomes	*<u>Changes in cognitive function from baseline to week 12 (MMSE; mean (SD))</u>*

	I = 4.96 (2.34) *C = 2.68 (1.52)* *MD (95% CI): 2.28 (1.16 to 3.4), t=4.091, p<0.001* *Rm GLM analysis showed a significant effect for treatment (F = 8.97, p-value = 0.004) and time × treatment (F = 11.00, p-value <0.001)* *Assessment of cognitive function (MoCA; mean (SD))* *I = 5.76 (1.74)* *C = 2.92 (1.44)* *MD (95% CI): 2.84 (1.93 to 3.75), t=6.288, p<0.001* *Rm GLM analysis showed a significant effect for treatment (F = 13.36, p-value = 0.001) and time × treatment (F = 20.5, p-value <0.001)* *Assessment of depression symptoms (HAM-D; mean (SD))* *I = −2.16 (1.46)* *C = −1.24 (1.23)* *MD (95% CI): −0.92 (−1.69 to −0.15), t= −2.403, p=0.020* *Rm GLM analysis showed a significant effect for time (F = 65.28, p-value <0.001) and time × treatment (F = 5.13, p-value = 0.014) but not for treatment on changes of HAM-D scores.* *Assessment of anxiety symptoms (HAM-A; mean (SD))* *I = − 0.8 (1.19)* *C = − 0.2 (0.5)* *MD (95% CI): −0.60 (−1.12 to−0.07), t= −2.324, p=0.027* *Rm GLM analysis indicated that time (F = 12.15, p:< 0.001) and time × treatment (F = 4.27, p-value = 0.031) had significant effects on changes of HAM-A scores.*
Comments Risk of bias	*Moderate*

Author Year Country Ref #	*Navas-Otero* *2024* *Spain* *[36]*
Study design Setting Population Follow up	*RCT, singel-blind* *Outpatient care* *Participants (>18 years) recruited from a regional long covid association with a diagnosis of long covid-19 syndrome (mean age apx 43–44 years, apx 80% female; average time since infection apx 18–20 months). Thus, population likely fulfilling the WHO criteria.* *6 weeks*
Intervention Participants (n) Drop-outs (n)	*A lifestyle adjustment program, based on symptom monitoring and recognition of symptomatology and on the other hand, adaptation and functional improvement* *27* *0*
Comparison Participants (n) Drop-outs (n)	*Control group. The control group intervention received the standard medical care, plus a leaflet with information about the main long COVID-19 symptoms* *27* *0*

Outcomes	*Outcome measures:* *<u>Quality of life (EQ-5D VAS).</u> The dimensions assessed:* • *Mobility, p for group comparison =0.74* • *Self-Care p for group comparison =0.004, in favour of active intervention* • *Daily Living p for group comparison =0.749* • *Pain/Discomfort p for group comparison =0.660* • *Anxiety/Depression, p for group comparison =0.009 in favour of active intervention* • *EQ-D5 VAS, p for group comparison =0.085* *<u>Disability (WHODAS 2.0):</u>* *Of seven subscales tested, one showed a statistically significant finding in favour of active intervention:* • *Selfcare p for group comparison =0.014* • *Total score WHODAS, p for group comparison =0.495* *<u>The impairment in functioning (WSAS):</u>* *Of five subscales tested, none showed a statistically significant finding.* *Total score for WSAS, p for group comparison =0.978*
Comments Risk of bias	*Multiple testings and no correction* *Moderate*

Author Year Country Ref #	*Ogonowska-Slodownik* *2023* *Poland* *[37]*
Study design Setting Population Follow up	*RCT* *Outpatient care* *Children 10 to 12 years old with symptoms typical of post COVID-19 condition, including fatigue and shortness of breath/respiratory issues, at least one month after an initial COVID-19 infection.* *After treatment (8 weeks)*
Intervention Participants (n) Drop-outs (n)	*AQUA - Aquatic aerobic exercises twice a week, 45 min per session, for eight weeks* *27* *2*
Comparison Participants (n) Drop-outs (n)	*LAND - Land based aerobic exercises twice a week, 45 min per session, for eight weeks* *29* *6*
Comparison Participants (n) Drop-outs (n)	*CONTROL – no exercise* *30* *4*
Outcomes	*Primary outcomes:* *<u>VO2 max [ml/kg/min] mean difference (95% CI) between groups post intervention</u>* *2.9 (–1.5 to 7.4)* *<u>HR max [beats/min] mean difference (95% CI) between groups post intervention</u>* *1.8 (–6.9 to 10.6)* *<u>VE [L/min] mean difference (95% CI) between groups post intervention</u>* *0.9 (–8.5 to 10.2)*

	OUES [L/min] mean difference (95% CI) between groups post intervention *0.04 (–0.3 to 0.4)* *OUES [ml/kg/min] mean difference (95% CI) between groups post intervention* *2.7 (–2.3 to 7.8)* *RER mean difference (95% CI) between groups post intervention* *0.003 (–0.02 to 0.03)* *CFSQ mean difference (95% CI) between groups post intervention* *1.2 (–3.6 to 6.1)* *Secondary outcomes:* *PedsQL children mean difference (95% CI) between groups post intervention* *4.3 (-2.8 to 11.5)* *PedsOL parent mean difference (95% CI) between groups post intervention* *7.2 (0.9 to 13.5)* *Additional outcomes were reported*
Comments Risk of bias	*A third group named control was included but participants were not identified the same way as for the other groups, nor were they included in the randomization.* *Moderate*

Author Year Country Ref #	*Ojeda* *2024* *Spain* *[38]*
Study design Setting Population Follow up	*RCT, single-blind* *Primary care setting* *Adult survivors (aged 65 (56–71) years, 73.5% male) from critically severe (confirmed) COVID-19 infection with at least one of the following inclusion criteria: 1) APACHE II score >14, 2) ICU stay >10 days, 3) acquired weakness in ICU, 4) delirium during ICU admission* *6 months*
Intervention Participants (n) Drop-outs (n)	*A follow up program, patient education on post-intensive care syndrome and pain, and a psychological intervention based on Rehm's self-control model in patients with abnormal depression scores (≥8) in the Hospital Anxiety and Depression Scale (HADS) at the baseline visit* *51* *8*
Comparison Participants (n) Drop-outs (n)	*Care as usual (follow-up appointments with their referring physicians (primary care physicians or specialists not directly involved in study). No preventive psychological intervention was administered to the patients as part of study.* *the study* *51* *8*
Outcomes	*Quality of life* *EQ VAS – intervention group;control group;p-value:* *Baseline: 70 (60 to 80); 75 (60 to 80); p=0.56* *3-month: 70 (63 to 80); 78 (60 to 80); p=0.6 – adjusted p-value: >0.99* *6-month: 80 (65 to 90); 80 (60 to 90); p=0.69 – adjusted p-value: >0.99* *EQ 5D/5L – intervention group; control group;p-value:*

	Baseline: 0.8 (0.6 to 0.9); 0.8 (0.6 to 0.9); p=0.18 *3-month: 0.9 (0.7 to 1); 0.8 (0.6 to 0.9); p=0.72 – adjusted p-value: >0.99* *6-month: 0.9 (0.7 to 1); 0.8 (0.6 to 1); p=0.09 – adjusted p-value: 0.86* *<u>Pain (BPI – first question*) intervention group; control group;p-value:</u>* *Baseline: 24 (53); 28 (55); p>0.99* *3-month: 20 (54); 23 (52); p>0.99 – adjusted p-value: >0.99* *6-month: 20 (47); 21 (49); p>0.99 – adjusted p-value: >0.99* *<u>Anxiety HADS-A intervention group; control group;p-value:</u>* *Baseline: 6 (12); 9 (20); p=0.4* *3-month: 8 (22); 7 (16); p=0.56 – adjusted p-value: >0.99* *6-month: 7 (16); 7 (17); p>0.99 – adjusted p-value: >0.99* *<u>Depression HADS-D intervention group; control group;p-value:</u>* *Baseline: 5 (10); 6 (13); p=0.51* *3-month: 5 (14); 9 (21); p=0.6 – adjusted p-value: >0.99* *6-month: 5 (12); 9 (22); p=0.6 – adjusted p-value: >0.99* *See study for additional results on BPI-SF average pain item, BPI-SF interference score, DN4, PCS, PTSD Checklist (PCL-5)* **''Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain?''*
Comments	
Risk of bias	*Moderate*

Author	*Okan*
Year	*2022*
Country	*Turkey*
Ref #	*[39]*
Study design	*RCT*
Setting	*Outpatient clinic and telerehabilitation in home environment*
Population	*Adults aged ≥18 years (44.6% female, mean age: 48.9 (intervention), 52.2 (control)) who had been previously (2 months prior) treated for COVID-19 pneumonia in hospital (9% ICU admitted)* *Not completely fulfilling WHO criteria for post COVID-19*
Follow up	*5 weeks*
Intervention	*Breathing exercises (respiratory control, pursed lip breathing, and diaphragmatic breathing exercises) 3/day for 5 weeks (one session performed via telemedicine each week).*
Participants (n)	*26*
Drop-outs (n)	*0*
Comparison	*A brochure explaining breathing exercises as above. The first practice session was performed face-to-face in hospital environment, similar to the intervention group. Patients recommended to practice a 20 to 30-minute light-intensity walk five times/week.*
Participants (n)	*26*
Drop-outs (n)	*0*
Outcomes	*Functional capacity* *<u>Group x time interaction 6MWT:</u>* *95% CI: 1.254–9.631, F=31.324, p3<0.001; pη2=0.646 – significant difference with large* estimated impact magnitude* *(two-way mixed-effect ANOVA analysis with post-hoc Bonferroni correction)*

	Pulmonary function *<u>Group x time interaction FEV1 %:</u>* *95% CI: 0.220–4.357, F=11.939, p3=0.001; pη2=0.193 – significant difference with large* estimated impact magnitude* *(two-way mixed-effect ANOVA analysis with post-hoc Bonferroni correction)* *<u>Group x time interaction FVC %:</u>* *95% CI: 0.221–3.568, F=13.815, p3=0.001; pη2=0.216 – significant difference with large* estimated impact magnitude* *(two-way mixed-effect ANOVA analysis with post-hoc Bonferroni correction)* *<u>Group x time interaction FEV1/FVC %:</u>* *Difference not significant* *<u>Group x time interaction MVV %:</u>* *(95% CI: 3.212–7.250, F=27.979, p3<0.001, pη2=.537) – significant difference* *(two-way mixed-effect ANOVA analysis with post-hoc Bonferroni correction)* **The value was considered small if it was 0.01≤η2<0.06, moderate if it was 0.06≤η2<0.14, and large if it was ≥0.14.*
Comments Risk of bias	 *Moderate*

Author Year Country Ref #	*Oliver-Mas* *2023* *Spain* *[40]*
Study design Setting Population Follow up	*RCT, double-blind* *Medical facility* *Patients (mean age 45.66±9.49 years, 78.72% female) with post-COVID fatigue (MFIS>50), 19% previously hospitalised* *1 month*
Intervention Participants (n) Drop-outs (n)	*Transcranial direct current stimulation (tDCS), 8 sessions (2 mA) á 20 minutes* *24* *0*
Comparison Participants (n) Drop-outs (n)	*Sham tDCS* *24* *0*
Outcomes	*Primary outcome:* *<u>Change in fatigue, rm ANOVA, time x group interaction</u>* *MFIS-total: not significant ($F_{(2,82)}$=1.730, p=0.184)* *MFIS-physical: <u>significant, favouring intervention</u> ($F_{(2,82)}$=3.517, p=0.034)* *MFIS-cognitive: not significant ($F_{(2,82)}$=0.55, p=0.496)* *MFIS-psychosocial: not significant ($F_{(2,82)}$=1.730, p=0.184)* *Secondary outcomes:* *Depression (BDI-II): <u>significant, favouring intervention (</u>$F_{(2,82)}$=3.447, p=0.036)*

	Executive function (Stroop – IG) and quality of life (EuroQoL-5D – VAS): non-significant results. *All the adverse events reported were mild and transient, with no differences between the active stimulation and sham stimulation groups.*
Comments Risk of bias	 *Moderate*

Author Year Country Ref #	*Palau* *2022* *Spain* *[41]*
Study design Setting Population Follow up	*RCT* *Home based inspiratory muscle training (IMT) program.* *Symptomatic adult aged >18 (median age 50.4±12.2, 42% female) with a previous admission due to SARS-CoV-2 pneumonia and at least 3 months after discharge.* *12 weeks, approximately*
Intervention Participants (n) Drop-outs (n)	*Base line physiotherapist assessment and education in home-based inspiratory training program consisting of twice daily 20 min inspiratory resistance training of 25%–30% of measured maximal inspiratory pressure for 12 weeks.* *13* *0*
Comparison Participants (n) Drop-outs (n)	*Usual care including baseline visit.* *13* *0*
Outcomes	*Primary outcome:* *Average change from baseline in mean peak VO_2:* *At 3 months, the mean of peakVO_2 was higher in those in the IMT group (22.2mL/kg/min; 95% CI, 21.3 to 23.2 vs 17.8mL/kg/min; 95% CI, 16.8 to 18.7; p<0.001)* *Secondary endpoint:* *Included dimensions in the Quality of life EQ-5D-3L tool:* *A significant improvement in usual activities (−0.31, 95% CI, −0.54 to −0.07, p=0.013) and anxiety/depression (−0.53, 95% CI, −0.67to −0.40, p<0.001) dimensions was found in IMT group with no significant changes in the usual care group.* *IMT resulted in a non-significant improvement in both groups' mobility, self-care and pain/discomfort dimensions.* *A significant change in the patient's self-rated health on the vertical VAS dimension in the IMT group (21.1, 95% CI, 12.9to 29.4, p<0.001)* *Additional outcomes were reported.*
Comments Risk of bias	 *Moderate*

Author Year Country Ref #	*Pleguezuelos* *2024* *Spain* *[42]*
Study design	*RCT, single blinded*

Setting	*Outpatients setting*
Population	*Participants recruited from hospital care (apx 57–73% hospitalized, apx 30–42% in ICU), aged >18 years, (mean age about 54 (SD 11) years, about 21% women) with confirmed previous acute COVID-19 infection, and presenting post-covid symptoms. The group did NOT fulfil the WHO-criteria at the time of inclusion.*
Follow up	*15 weeks (also evaluated at 3 months and 12 months (detraing)*
Intervention	*A supervised homebased telerehabilitation program combining aerobic and strength exercises three times weekly for 15 weeks.*
Participants (n)	*75*
Drop-outs (n)	*9*
Comparison	*No supervised telerehabilitation. Participants in control group were asked to carry out their routine daily life activities*
Participants (n)	*75*
Drop-outs (n)	*10*
Outcomes	*Primary outcome:* *Cardiopulmonary exercise test performed on ergometric bicycle (several tests performed)* *Exercise capacity (exercise time in seconds):* *An intervention × time interaction effect was detected (p=0.001) in favour of intervention* *Peak oxygen uptake (V02):* *No intervention × time interaction effect or main intervention effect was observed in the relative V̇O2peak (p>0.05)* *Power output (Watts):* *In power output (Figure 3C), an intervention × time interaction effect was found (p<0.001)* *Mechanical efficiency:* *In delta efficiency an intervention × time interaction effect was detected (p=0.001)* *Additional outcomes were reported*
Comments	
Risk of bias	*Moderate*

Author	*Philip*
Year	*2022*
Country	*UK*
Ref #	*[43]*
Study design	*RCT*
Setting	*Outpatient setting.*
Population	*Participants recovering from COVID-19 (mean age 49 (SD 12) years, 81% women) with ongoing breathlessness, with or without anxiety, ≥4 weeks after symptom onset (the study population, thus, does not fulfil the WHO-criteria for post COVID-19)*
Follow up	*6 weeks.*
Intervention	*The English National Opera Breathe programme, breathing retraining using singing techniques (6 weeks, online).*
Participants (n)	*74*
Drop-outs (n)	*16*
Comparison	*Care as usual*
Participants (n)	*76*
Drop-outs (n)	*5*

Outcomes	*Primary outcome:* *<u>Change in HRQoL, baseline – end of 6-week course, assessed by SF-36, MHC and PHC score</u>* *Compared to usual care, ENO Breathe was associated with an improvement in MHC score (regression coefficient 2.42 (95% CI, 0.03 to 4.80), p=0.047), but not PHC score (0.60, –1.33 to 2.52, p=0·54).* *<u>VAS for breathlessness (running):</u>* *Favoured ENO Breathe participation: –10.48 (–17.23 to –3.73), p=0.0026* *No other statistically significant between-group differences in any other secondary outcome were observed.*
Comments Risk of bias	*The study population does not fulfil the WHO-criteria for post COVID-19* *Moderate*

Author Year Country Ref #	*Rasmussen* *2023* *Denmark* *[44]*
Study design Setting Population Follow up	*Investigator blinded RCT* *Outpatient* *Persons (mean age 57.2 (SD 10) years, 32% women) previously hospitalized for laboratory confirmed SARS-CoV-2, but no specific symptoms were required.* *12 weeks*
Intervention Participants (n) Drop-outs (n)	*High-intensity interval training (HIIT) program with three 38 minutes supervised and individualized work out sessions including every week on bicycle ergometer with the aim to improve cardiorespiratory fitness* *14* *1*
Comparison Participants (n) Drop-outs (n)	*Standard care* *14* *1; 4 participants engaged in exercise program*
Outcomes	*The primary outcome was left ventricular mass measured with MRI, not reported here.* *Secondary outcomes included:* *<u>Lung function, measured with with spirometry.</u>* *There were no statistically significant differences in between group comparisons for predictive values of FEV1, FVC, TLC and RV.* *<u>Functional capacity and HRQoL</u>, measured with Post-COVID-19 functional scale PCFC* *In terms of PCFS, similar proportions reported no functional limitations (PFCS 0) at baseline. At follow-up, this proportion had almost doubled in the HIIT group, whereas the proportion in the standard care group was similar as baseline.* *<u>Strength testing</u>* *Upper and lower body strength were assessed by one-repetition maximum tests (the maximum amount of weight that can be lifted once with proper form through full range of motion, 1RM) in chest press- and leg press machines. Wmax and leg press 1RM increased similarly in both groups, whereas chest press 1RM was improved in the intervention group only, and there were no notable between group changes in body composition.* *<u>Physical activity level</u>*

	Posture and physical activity behaviors are measured using three axial accelerometer-based physical activity monitors. *Step counts per day and time spent at moderate/ high activity level changed in the HIIT group from baseline. However, time spent being inactive concurrently decreased in the HIIT group compared with the control group (ns).* *Several additional outcomes were reported*
Comments	
Risk of bias	*Moderate*

Author	*Romanet*
Year	*2023*
Country	*France*
Ref #	*[45]*
Study design	*Open assessor blinded multicenter RCT*
Setting	*Outpatient program setting*
Population	*Population (mean age 58 (SD 12) years, women 38%) with persistent respiratory symptoms after CARDS. Participants fulfilled WHO criteria for post COVID-19 (long covid)*
Follow up	*12 weeks*
Intervention	*Exercise training rehabilitation (ETR) including both endurance and strength training for pulmonary rehabilitation,2 x 60 minutes per week for 12 weeks. Power intensity was adjusted according to each participant's progress until the target heart rate and dyspnea were reached.*
Participants (n)	*27*
Drop-outs (n)	*0 (4 chose standard physiotherapy during follow up)*
Comparison	*Standard usual care during the 90 days and received standard physiotherapy at the rate of 2 x 30 min sessions per week for 10 weeks.*
Participants (n)	*33*
Drop-outs (n)	*0 (3 chose endurance training during follow up)*
Outcomes	*Primary outcome:* *Measurement of dyspnea in its 3 dimensions, as assessed by the difference in the multidimensional dyspnea profile (MDP) score.* *Mean difference (95% CI) between-groups at 90 days:* *MDP total score: –18.61 (–27.78 to -9.44), p<0.0001, in favour of intervention.* *Breathing discomfort: –1.74 (–2.81 to –0.67), p=0.0006, in favour of intervention.* *Sensory dimension: –9.92 (–14.67 to –5.18), p<0.0001, in favour of intervention.* *Secondary outcomes:* *Measurement of functional dyspnoea (mMRC scale).* *Mean difference (95% CI) between-groups at 90 days:* *mMRC: –0.76 (–1.21 to –0.30), 0.001, in favour of intervention* *Measurement of HRQoL (SF-12) at 90 days* *SF-12 total score: 8.24, 95% CI (0.22 to 16.25), p=0.14, in favour of intervention* *Additional outcomes were reported*
Comments	
Risk of bias	*Moderate*

Author	*Samper-Pardo*
Year	*2023*

Country	*Spain*
Ref #	*[46]*
Study design	*RCT, open-label*
Setting	*Primary health care*
Population	*Adults aged ≥18 (80% female, mean age 48.28±9.26) with confirmed COVID-19 diagnosis >12 weeks prior and with persistent long covid symptoms.*
Follow up	*3 months*
Intervention	*ReCOVery APP (with rehabilitative content and attended three sessions on motivational methodology, APP management, and strengthening of their personal constructs; health literacy, self-efficacy, and personal activation), in addition to treatment as usual established by their general practitioner*
Participants (n)	*52*
Drop-outs (n)	*7*
Comparison	*Treatment as usual established by their general practitioner*
Participants (n)	*48*
Drop-outs (n)	*6*
Outcomes	*Primary outcome: quality of life* *<u>SF-36 Physical health, 3 month follow-up – baseline, mean (SD)</u>* *I: 4.56 (12.14)* *C: 8.02 (14.38)* *p=0.234* *CI (–9.20 to 2.28)* *<u>SF-36 Mental health, 3 month follow-up – baseline, mean (SD)</u>* *I: 5.07 (16.10)* *C: 3.20 (18.27)* *p=0.615* *CI (–5.49 to 9.23)* *Secondary outcomes:* *<u>Cognitive domains (memory, attention, language, or working memory measured with MoCA), 3 month follow-up – baseline, mean (SD)</u>* *I: 0.91 (4.24)* *C: 0.30 (2.87)* *p=0.439* *CI (–0.93 to 2.14)* *<u>Physical functioning (30 s Sit-to-stand test) 3 month follow-up – baseline, mean (SD)</u>* *I: 0.32 (2.24)* *C: –0.28 (4.84)* *p= 0.806* *CI (–1.36 to 1.06)* *<u>Affective status (measured with HADS) 3 month follow-up – baseline, mean (SD)</u>* *I: –0.28 (4.84)* *C: –1.21 (6.17)* *p=0.441* *CI (–1.45 to 3.30)* *<u>Sleep quality (measured with ISI) 3 month follow-up – baseline, mean (SD)</u>*

	I: –0.54 (5.35) *C: –1,47 (5.94)* *p=0.449* *CI (–1.50 to 3.36)*
Comments Risk of bias	 *Moderate*

Author Year Country Ref #	*Sánchez-Milá* *2023* *Spain* *[47]*
Study design Setting Population Follow up	*RCT* *Primary care setting* *Adults 18–65 years (mean age in treatment group 1: 24 (14 SD) years, in treatment group 2: 40 (SD 22) years, women about 50%), >5 months since medically diagnosed COVID-19 with symptoms such as dyspnea or fatigue* *Mid-term (15 days) and after treatment (31 days)*
Intervention Participants (n) Drop-outs (n)	*Respiratory treatment based on inspiratory muscle training using PowerBreathe for 31 days* *103* *3*
Comparison Participants (n) Drop-outs (n)	*Treatment based on traditional diaphragmatic exercises prescribed in various respiratory conditions for 31 days* *104* *4*
Outcomes	*Main outcomes:* *<u>FVC (liters) post treatment, mean (SD):</u>* *I: 4.0255 (0.10994)* *C: 3.5408 (0.08307)* *p < 0.001 (based on group x time effect)* *<u>FEV1 (liters) post treatment, mean (SD):</u>* *I: 3.6177 (0.31406)* *C: 2.9529 (0.08729)* *p < 0.001 (based on group x time effect):* *<u>FEV1/FVC (%) post treatment, mean (SD):</u>* *I: 73.2897 (3.57746)* *C: 69.9542 (1.17489)* *p < 0.001 (based on group x time effect)* *<u>PEFR (liters/min) post treatment, mean (SD):</u>* *I: 8.0926 (0.21457)* *C: 7.5725 (0.24420)* *p < 0.001 (based on group x time effect)* *<u>FIVC (liters) post treatment, mean (SD):</u>* *I: 2.3745 (0.22702)* *C: 2.0859 (0.11724)*

	p < 0.001 (based on group x time effect) *<u>MIP cmH2O post treatment, mean (SD):</u>* *I: 91.1064 (4.67964)* *C: 79.3713 (3.73998)* *p < 0.001 (based on group x time effect)* *Other outcomes:* *<u>Systolic pressure (mmHg) post treatment, mean (SD):</u>* *I: 122.29 (4.680)* *C: 133.94 (3.250)* *p < 0.001 (based on group x time effect)* *<u>Dyastolic pressure (mmHg) post treatment, mean (SD):</u>* *I: 72.49 (43.82)* *C: 78.69 (6.324)* *p < 0.001 (based on group x time effect)* *<u>Dyspnea Borg post treatment, mean (SD):</u>* *I: 1.03 (0.784)* *C: 3.02 (0.791)* *p < 0.001 (based on group x time effect)* *<u>Lower limbs borg post treatment, mean (SD):</u>* *I: 1.00 (0.816)* *C: 1.58 (1.093)* *p = 0.002 (based on group x time effect)* *<u>Oxygen Saturation (mmHg) post treatment, mean (SD):</u>* *I: 97.52 (1.141)* *C: 97.62 (1.117)* *p = 0.841 (based on group x time effect)* *<u>Cardiac Frequency (BPM) post treatment, mean (SD):</u>* *I: 86.16 (2.505)* *C: 85.93 (2.571)* *p = 0.969 (based on group x time effect)* *<u>6MWD (meters) post treatment, mean (SD):</u>* *I: 595.44 (46.302)* *C: 603.26 (50.572)* *p = 0.203 (based on group x time effect)*
Comments	*Considerate age difference between group despite randomization*
Risk of bias	*Moderate*

Author	*Santana*
Year	*2023*
Country	*Brazil/USA*
Ref #	*[48]*
Study design	*RCT, double-blind*
Setting	*Department of Rehabilitation at University Medical Center*

Population	*Adults aged 18–80 years (mean age 51.63±15.87 (intervention) and 54.46±19.01 (control), 64.3% female) with diagnosis of PASC-related fatigue, followed in an outpatient clinic, 73% home-isolated with symptoms in acute phase.*
Follow up	*5 weeks*
Intervention	*3 mA HD-tDCS targeting left primary motor cortex (M1), 30 min paired with individually tailored rehabilitation program.* *2 sessions/week over 5 weeks.*
Participants (n)	*35*
Drop-outs (n)	*0*
Comparison	*Sham HD-tDCS paired with rehabilitation program*
Participants (n)	*35*
Drop-outs (n)	*0*
Outcomes	*Fatigue severity, assessed by MFIS-scale:* The intervention group had significantly greater reduction in fatigue compared to sham at the end of the 5-week intervention. Mean group difference: 14.03; effect size: 1.2 (95% CI, 7.78 to 20.28; p<.001) *MFIS-subscales* Reduction in fatigue was found in both cognitive (mean group difference: 8.29; effect size: 1.1, 95% CI, 3.56 to 13.01; p< .001) and psychosocial subscales (mean group difference: 2.37; effect size 1.2, 95% CI, 1.34 to 3.40; p< .001). No difference was observed between groups on physical fatigue (mean group difference: 0.71 points; effect size 0.1 (95% CI, 4.47 to 5.90; p=.09)). *Anxiety (HAM-A)* *Favoures intervention group (mean group difference: 4.88; effect size: 0.9 (95% CI, 1.93 to 7.84; p<.001))* *Quality of life (WHOQOL-bref)* *Favoures intervention group (mean group difference: 14.80; effect size: 0.7; (95% CI, 7.87 to 21.73; p<.001))* *Pain (MPQ)* *No significant difference between groups (mean group difference: 0.74; no effect size (95% CI, 3.66 to 5.14; p=.09)* *The proportion of clinically improved participants was significantly larger in the intervention group compared to sham group (77.14% vs 45.71%; NNT ¼ 3; odds ratio ¼ 0.24; 95% CI, 0.08e0.70; P<.001)*
Comments Risk of bias	Moderate

Author	*Schepens*
Year	*2022*
Country	*The Netherlands*
Ref #	*[49]*
Study design	*RCT, double-blind*
Setting	*Self-administration outside health care setting*
Population	*Adults >18 years old (median age 49 years (IQR 41–57, range 20–78), 63.5% female) with persistent (>4 weeks) olfactory disorders within 12 weeks after confirmed COVID-19*
Follow up	*12 weeks post start of treatment*
Intervention	*Oral prednisolone, 40 mg capsules once daily for 10 days*
Participants (n)	*58*

Drop-outs (n)	*1*
Comparison Participants (n) Drop-outs (n)	*Placebo capsules once daily for 10 days* *57* *1*
Outcomes	*Outcomes at 12 weeks:* *Sniffin' Sticks test TDI score (range 1-48), mean (SD)* *I: 28.8 (24–30.9)* *C: 26.8 (23.6–29.3)* *MD (95% CI): –1.5 (–3.0 to 0.25), p=0.10* *Taste Strip Test total score (range 0-16), mean (SD)* *I: 11 (9–13)* *C: 11 (9.3–13)* *MD (95% CI): 0.00 (–1.00 to 1.00), p=0.50* *Olfactory Disorders Questionnaire, total score (range 0.13-1.00), mean (SD)* *I: 0.4 (0.3–0.5)* *C: 0.4 (0.3–0.6)* *MD (95% CI): 0.00 (–0.06 to 0.06), p= 0.89* *Sense of smell, VAS (range 0-10), mean (SD)* *I: 3.6 (1.0–5.8* *C: 3.2 (1.8–6.5)* *MD (95% CI): 0.3 (–0.9 to 1.3), p=0.53* *Sense of taste, VAS (range 0-10), mean (SD)* *I: 5.0 (2.0–7.8)* *C: 5.6 (2.3–7.6)* *MD (95% CI): 0.1 (–1.00 to 1.3), p=0.80* *Trigeminal sensations, VAS (range 0-10), mean (SD)* *I: 5.3 (2.4–7.9)* *C: 5.1 (2.9–7.4)* *MD (95% CI): –0.2 (–1.3 to 1.00), p=0.76* *Adverse events, number of events:* *I: 3* *C:0*
Comments Risk of bias	 *Low*

Author Year Country Ref #	*Shamohammadi* *2021* *Iran* *[50]*
Study design Setting Population Follow up	*RCT, double-blind* *Primary care/ home-based* *Men aged 30–50 (mean age 41.37±2.34 (intervention) and 39.23±2.45 (control)), outpatients with ED following recovery from COVID-19 without acute respiratory distress syndrome and with negative PCR test.* *3 months post study start*
Intervention	*Tadalafil, 5 mg daily for 3 months*

Participants (n)	*35*
Drop-outs (n)	*3*
Comparison	*Placebo*
Participants (n)	*35*
Drop-outs (n)	*5*
Outcomes	*International Index of Erectile Function (IIEF-5), MD change from baseline* *Erectile function p=0.001, favours intervention* *Overall satisfaction p=0.001, favours intervention* *Additional subscales are reported*
Comments	*Clinical relevance uncertain.*
Risk of bias	*Low*

Author	*Tosato*
Year	*2022*
Country	*Italy*
Ref #	*[51]*
Study design	*RCT, single-blind*
Setting	*Post-acute COVID-19 outpatient clinic*
Population	*Adults aged 20–60 (median age 50.5 (IQR 14.0), 65.2% female) with previous COVID-19 infection with persistent fatigue (Response "most or all the time" to item seven on CES-D), 56.5% previously hospitalised.*
Follow up	*28 days*
Intervention	*Oral supplementation 1.66 g L-arginine plus 500 mg liposomal vitamin C, 2/day for 28 days*
Participants (n)	*25*
Drop-outs (n)	*2*
Comparison	*Placebo*
Participants (n)	*25*
Drop-outs (n)	*2*
Outcomes	*Distance walked on the 6 min walk test (median (IQR) change from baseline)* *I: +30.0 (40.5) m* *C: +0.0 (75.0) m* *p=0.001* *Mean difference=50 m, 95% CI, 20.0 to 80.0 m; effect size=0.56* *See study for more results on secondary outcomes: handgrip strength, flow-mediated dilation, and fatigue persistence*
Comments	
Risk of bias	*Moderate*

Author	*Yan*
Year	*2023*
Country	*US*
Ref #	*[52]*
Study design	*RCT*
Setting	*Outpatient setting.*
Population	*Participants (mean age 44.1 years±14.0, 50% female) with PCR–confirmed diagnosis of severe acute COVID-19 with objective olfactory dysfunction between 6–12 months after acute infection.*
Follow up	*4 and 12 weeks. Only 12-weeks results are reported below.*

Intervention Participants (n) Drop-outs (n)	*Three intranasal injections with platlet rich plasma at two sites within the olfactory cleft along the superior septum, posterior to the head of the middle turbinate.* *18* *4*
Comparison Participants (n) Drop-outs (n)	*Three intranasal injections with placebo (sterile saline) bilaterally in the same locations as in the intervention group.* *12* *12*
Outcomes	*Primary outcome:* *<u>Change in TDI using Sniffin' Sticks, results between groups:</u>* *Total change in TDI: 3.67 95%CI (0.05 to 7.29), p=0.047* *T score: 0.07 95%CI (–1.71 to 1.85), p=0.935* *D score: 2.40 95%CI (0.80 to 4.00), p= 0.004* *I score: 1.12 95%CI (–0.76 to 3.00) p=0.239* *Secondary outcomes:* *<u>Responder rate at 3 months (where a responder was defined as a clinically significant improvement on Sniffin' Sticks TDI score, ≥5.5 points):</u>* *By completion of trial the responder rate was 8.3% in the placebo arm (1 of 12) compared to 57.1% (8 of 14) of subjects in the PRP arm (OR 12.5 (95% exact bootstrap CI, 2.2–116.7))* *<u>VAS:</u> 0.88, (95% CI, –0.38 to 2.15), p=0.167* *Additional outcomes were reported*
Comments Risk of bias	 *Moderate*

Author Year Country Ref # Authour Year Country Ref #	*Zilberman-Itskovich* *2022* *Israel* *#1251* *Leitman* *2023* *Israel* *[53]*
Study design Setting Population Follow up	*RCT, double-blind* *Medical facility* *Adults ≥18 years (mean age 48.4±10.6 years (intervention) and 47.8±8.5 years (control), 60.3% females) with persistent cognitive symptoms affecting quality of life >3 months following confirmed COVID-19 infection (16% previously hospitalised during acute phase of infection)* *1–3 weeks after last treatment session*
Intervention Participants (n) Drop-outs (n)	*HBOT in a multi-place Starmed-2700 chamber (HAUX, Germany), 40 daily sessions, 5 sessions per week within a 2-month-period.* *<u>HBOT protocol:</u>* *100% oxygen by mask at 2ATA for 90 min, 5-minute air breaks every 20 min.* *Compression/decompression rates 1.0 m/min.* *40* *3*
Comparison	*<u>Sham protocol:</u>*

	21% oxygen by mask at 1.03 ATA for 90 min. To mask controls, the chamber pressure was raised up to 1.2 ATA during the first 5 minutes along with circulating air noise, followed by decompression (0.4 m/min) to 1.03 ATA during next 5 minutes
Participants (n)	*39*
Drop-outs (n)	*3*
Outcomes	*Results presented as Cohen's d net effect size and p-value (p<0.05 was considered significant)* *<u>Cognitive assessment</u>:* *Cognitive score: d=0.495, p=0.038 (significant)* *Attention: d=0.477, p=0.045* *Executive function: d=0.463, p=0.052 (significant)* *Memory: d=0.111, p=0.636* *Information processing speed: d= 0.303, p=0.200* *Motor skills: d=0.338, p=0.154* *(Mindstreams computerized cognitive testing battery (NeuroTrax Corporation, Bellaire, TX))* *<u>Quality of life (SF-36):</u>* *Physical functioning: d=–0.269, p=0.254* *Physical limitations: d=0.546, p=0.023 (significant)* *Emotional limitations: d=0.215, p=0.361* *Energy: d=0.522, p=0.029 (significant)* *Emotional wellbeing: d=0.459, p=0.054* *Social function: d=0.391, p=0.099* *Pain domain: d=0.254, p=0.281* *General health domain: d=0.338, p=0.153* *<u>Olfactory and gustatory function:</u>* *No significant group-by-time interactions.* *See study for additional results on sleep quality (PSQI, Global=significant), psychological symptoms (BSI-18, Total=significant), pain (BPI, Pain interference=significant), pulmonary function (spirometry=<u>not</u> significant)* *<u>Cardiac function:</u>* *Global longitudinal strain (GLS), %: d=0.245, p=0.041* *Other cardiac outcomes (Global Work Index, Global Constructive Work, Global Wasted Work, Global Work Efficacy) were non-significant*
Comments	*Cardiac function outcomes are reported in a separate publication (Leitman et al 2023, #1278)*
Risk of bias	*Low for cognitive and most other outcomes,Some concerns for cardiac outcomes*

Abbreviations

ADLs = Activities of daily living; **AE** = Adverse events; **apx** = approximately; **A-PASC** = Post-COVID-19 Symptoms Assessment Questionnaire; **AQoL-6D** = Assessment of Quality of life—six dimensions; **ATA** = Atmospheres absolute (pressure); **BP** = Blood pressure; **bpm** = Beats per minute; **BDI-II** = Beck depression inventory; **BPI** = Brief pain inventory*;* **BSI-18** = Behavioural symptoms inventory-18 global score index; **BTT** = Butanol threshold test; **C** = Control; **CARDS** = COVID-19-associated Acute Respiratory Distress Syndrome; **CAU** = Care as usual; **CCCRC test score** = Connecticut Chemosensory Clinical Research Center test score; **CES-D** = Center for Epidemiological Studies Depression Scale; **CG** = Control group; **CGI**= Clinical Global Impression Scale; **CGI-C** = Clinical global impression of change; **CIS-conc** = Concentration subscale of Checklist individual strength; **CIS-fatigue** = Fatigue severity subscale of the Checklist Individual Strength; **COMPASS 31** = Composite Autonomic Symptom Score; **CRP** = C-reactive protein; **DDAVP** = Desmopressin; **DN4** = Douleur Neuropathique en 4 Questions; **DSC** = Dynamic Susceptibility Contrast; **DSST** = Digit Symbol Substitution Test; **DTI** = Diffusion Tensor Imaging; **ED** = Erectile dysfunction; **ET** = Exercise therapy; **EQ-5D-5L** = EuroQol-5 dimension-5-Level group; **FAI** = Fatigue Assessment Inventory; **FAS** = Fatigue Assessment Scale; **FEV** = Forced expiratory volume; **FEV1** = Forced expiratory volume in the first second; **FIS** = Fatigue Impact Scale; **FSS** = Fatigue severity scale; **FVC** = Forced vital capacity; **GAD-7**: Generalized Anxiety Disorder 7-item scale; **GLM** = General linear model; **GPAQ** = WHO Global Physical Activity Questionnaire; **h** = Hour(s); **HADS** = Hospital Anxiety and Depression Scale; **HADS-A** = Hospital Anxiety and Depression Scale anxiety subscale; **HADS-D** = Hospital Anxiety and Depression Scale depression subscale; **HAM-A** = Hamilton anxiety rating scale; **HBOT** = Hyperbaric oxygen treatment; **HUTT** = Head-up tilt table test*;* **HR** = Heart rate; **hrs** = Hours; **HRQoL** = Health-related quality of life; **I** = Intervention; **iCEPT** = Invasive cardiopulmonary exercise test; **ICU** = Intensive care unit; **IG**= Intervention group; **IIEF-5** = International Index of Erectile Function; **IPAC** = International Physical Activity Questionnaire; **IQR** = Interquartile range; **ISI** = Insomnia Severity Index; **ITT** = Intention to treat; **K-BILD** = King's Brief Interstitial Lung Disease questionnaire; **KW** = Kruskal-Wallis test; LCADL = **London Chest Activity of Daily Living Scale**; **LS MD** = Least squares mean difference; **LUT** = Luteolin; **m** = Meter; **MCS** = Mental Component Summary score of Short Form-36 Health Survey (SF-36); **MD** = Mean difference; **MDBS** = Modified Borg Dyspnea Scale; **MFIS** = Modified fatigue impact scale; **MICE** = Multiple imputation by chained equations*;* **MMSE** = Mini Mental State Examination; **mMRC** = Modified British Medical Research Council dyspnoea scale; **MMV** = Maximal voluntary ventilation; **MoCa** = Montreal Cognitive Assessment; **MPQ** = McGill pain questionnaire; **MRI** = Magnetic Resonance Imaging; **N/n** = Antal; **NE** = Norepinephrine; **ηp 2** = Partial eta-squared effect size; **NP-PASC** = Neuropsychiatric Post-acute sequelae of Sars-CoV-2 infection; **NRSI** = Non-randomized studies of interventions; **ns**=Not statistically significant; **OD** = Olfactory dysfunction*;* **OIQ** = Orthostatic intolerance questionnaire*;* **OR** = Odds ratio; **OT** = Olfactory training*;* **PASC** = Post-acute sequelae of Sars-CoV-2 infection; **PACSQ-14** = Post-acute COVID-19 syndrome 14-item improvement questionnaire*;* **PCC** = Post-covid(-19) conditions; **PCFS** = Post-COVID-19 functional Status scale; **PCL-C** = Post-traumatic Stress Disorder (PTSD) Checklist: Civilian; **PCL-5** = Posttraumatic Stress Disorder Checklist (version 5); **PCR** = Polymerase chain reaction; **PCS** = Pain Catastrophizing Scale; **PEA** = Palmitoylethanolamide; **PGIC** = Patient Global Impression of Change; **PHQ-9** = Patient Health Questionnaire; **PHQ-15** = Patient Health Questionnaire; **PICO** = Framework for structuring a research question by defining the Population, Intervention, Control and Outcomes; **QIDS-SR-16** = Quick Inventory of Depressive Symptomatology; **QOD-NS** = Questionnaire of olfactory disorder-negative statement; **QoL** = Quality of Life; **POTS**=Postural tachycardia syndrome; **PQSI** = Pittsburgh Sleep Quality Index; **PSP** = Primary care physician; **PSS** = Perceived Stress Scale; **PTSD checklist** = Post-traumatic stress disorder checklist; **PTSS** = Post-traumatic stress symptoms; **RAND SF-36** = RAND 36 Item Short Form Health Survey SF-36; **RCT** = Randomised controlled trial; **Rm ANOVA** = Repeated measures ANOVA; **RT-PCR** = Reverse transcription polymerase chain reaction; **RV**=Residual Volume, **s** = second(s); **SAS** = Self-rating Anxiety Scale; **SBP** = Systolic blood pressure; **SD** = Standard deviation; **SDS** = Self-rating Depression Scale; **SE** = Standard error; **SEM** = Standard error of mean; **SF-36** = Short form health survey-36; **SF-12** = Short form health survey-12; **SF-12 MCS** = Short form health survey-12 Mental component score; **SF-12 PCS** = Short form health survey-12 Physical component score; **SGRQ** = St George's Respiratory Questionnaire; **SIT** = Smell identification test; **6MWD** = 6 minute walking distance test; **6MWT** = 6 minute walking test; **SOC** = Standard of care; **SPC** = Summary of products characteristics; **Stroop – IG**: Stroop interference – index of golden; **TDI score** = Sum of results obtained for odour Threshold, Discrimination, and Identification; **tDCS** = Transcranial direct current stimulation; **TLC**=Total Lung Capacity; **Tph** = Tukey post-hoc test; **TSPP** = Tetrasodium Pyrophosphate; **UPSIT** =University of Pennsylvania Smell Identification Test; **VAS** = Visual analogue scale; **VO_2** = Oxygen uptake; **VO_{2PEAK}** = Peak oxygen consumption; **WHO-5** = The World Health Organisation-Five Well-Being Index; **WHODAS 2.0** = World Health Organization Disability Assessment Schedule; **WHOQOL-brief** = The World Health Organization Quality of Life Brief Version; **WSAS** = Work and Social Adjustment Scale

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